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A Radical Cascade Approach to the Skeleton of α -Cyclopiazonic Acid

Russell S. Craft

**A Thesis Submitted for the Degree of
Doctor of Philosophy**

**School of Life Sciences
Department of Chemistry
June 2009**

I hereby declare that this thesis has not been submitted, either in the same or different form, to this or any other University for a degree.

Signature:.....

To *My Mother*

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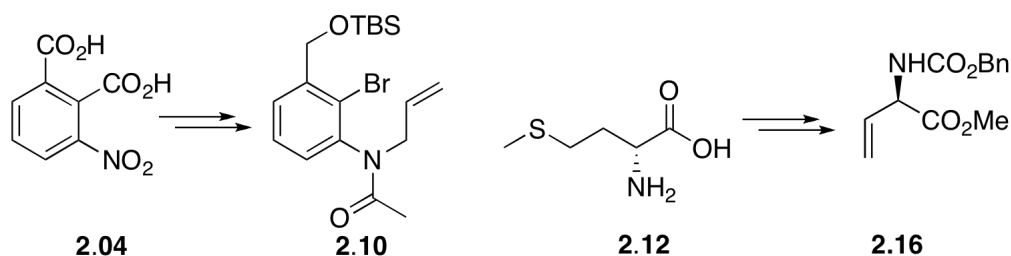
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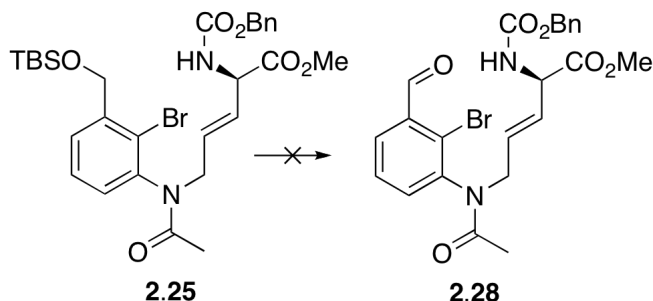
Abstract

A Radical Cascade Approach to the Skeleton of α -Cyclopiazonic Acid.

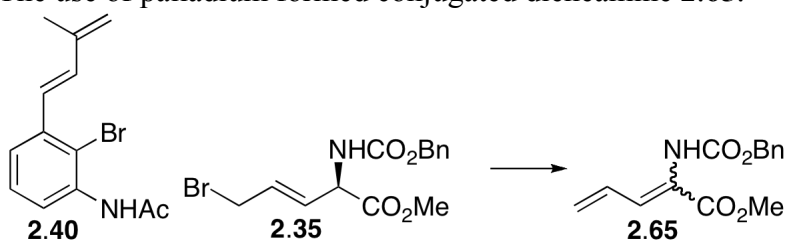
3-Nitrophthalic acid **2.04** was transformed into **2.10** in 38% yield. Vinylglycine derivative was synthesised from *D*-Methionine **2.12** in 42% yield.



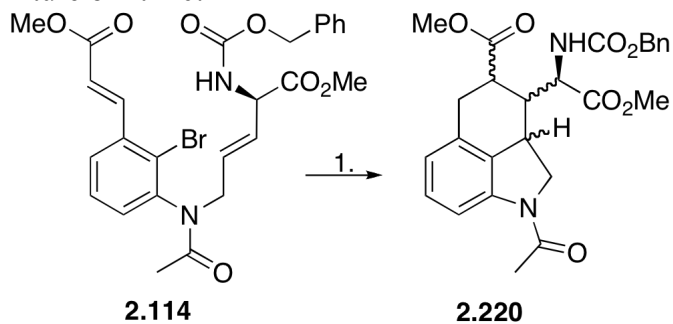
Compounds **2.10** and **2.16** were coupled using Grubbs' 2nd generation catalyst creating **2.25**. Unfortunately attempts to oxidise the benzylic position were unsuccessful.



An alternative approach was investigated using diene **2.40** derived from a precursor to **2.10** and allyl bromide **2.35**. Attempts to displace bromide under anionic conditions were futile. The use of palladium formed conjugated dieneamine **2.65**.



Deprotection, oxidation and elaboration of **2.10** prior to cross metathesis allowed the synthesis of **2.114**, which when subjected to radical conditions, formed a diastereomeric mixture of **2.220**.



Reagents and Conditions: 1) TBTH, AIBN, PhMe, 110°C, 74%

Abbreviations

Å	Ångstrom
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
aq	aqueous
Ar	aromatic
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
b.p.	boiling point
Bu	butyl
^t Bu	<i>tert</i> -butyl
ⁿ Bu	butyl
Bz	Benzoyl
°C	degrees Celsius
cat.	catalytic
Cbz	benzyloxycarbonyl
CDI	1,1'-carbonyldiimidazole
cm	centimetre
CM	cross-metathesis
conc.	concentrated
conv.	conversion
α -CPA	α -cyclopiazonic acid
CSA	camphorsulphonic acid
Cy	cyclohexyl
dba	dibenzylideneacetone
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
DCC	1,3-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminium hydride
DIPHOS	bis(diphenylphosphino)ethane
DMAP	4-dimethylaminopyridine

DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dppp	1,3-bis(diphenylphosphino) propane
dr	diastereomeric ratio
E ⁺	electrophile
e.e.	enantiomeric excess
EI ⁺	electron impact
ESI	electrospray ionisation
Et	ethyl
eq.	equivalents
g	gram(s)
HMPA	hexamethylphosphoric triamide
HOMO	Highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
Hz	Hertz
IR	infrared spectroscopy
KHMDS	potassium hexamethyldisilazide
Kg	kilograms
LDA	lithium di- <i>iso</i> -propylamide
LHMDS	lithium hexamethyldisilazide
M	molar
Me	methyl
MeOH	Methanol
Mes	mesitylene
min.	minute(s)
mL	millilitre
mol	mole
mmol	millimole
m.p.	melting point
Ms	methanesulfonyl

M.S.	molecular sieve
MS	mass spectrometry
MW	molecular weight
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMR	nuclear magnetic resonance
NMO	4-methylmorpholine <i>N</i> -oxide
Nu-	nucleophile
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
^{<i>i</i>} Pr	<i>iso</i> -propyl
pyr	pyridine
RCM	ring closing metathesis
ROMP	ring-opening metathesis polymerization
R _f	retention factor
rt	room temperature
SM	starting material
TBAB	Tetra Butyl Ammonium Bromide
TBAF	tetrabutylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBHP	<i>tert</i> -butyl hydroperoxide
TBS	<i>tert</i> -butyldimethylsilyl
TBTH	tributyltin hydride
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	toluene
Ts	tosyl

Introduction

1.1 Background

The indolic pentacyclic alkaloid α -cyclopiazonic acid (α -CPA) **1** is a mycotoxigenic secondary metabolite of the fungus *Penicillium cyclopium* Westling;¹ it has global distribution, frequently isolated from stored grains and cereals.^{2, 3} There have been reports of outbreaks of disease upon ingestion of feed contaminated with *P. cyclopium*.⁴

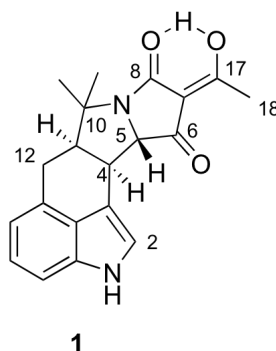


Figure 1: Structure of α -Cyclopiazonic Acid **1**.

Hozapfel determined its structure through a series of chemical degradations and found two structurally related metabolites α -cyclopiazonic acid imine **2** and β -cyclopiazonic acid **3**.⁵

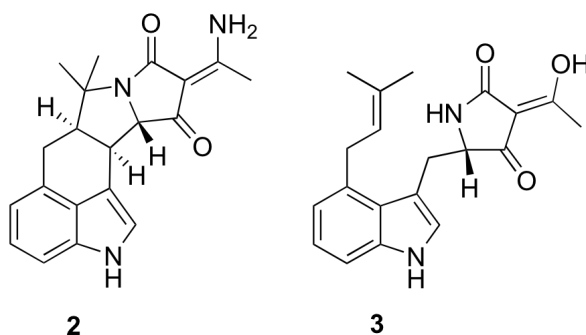
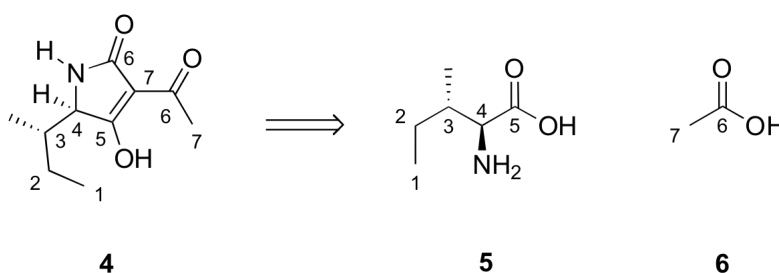


Figure 2: Structure of α -Cyclopiazonic Acid Imine **2** and β -Cyclopiazonic Acid **3**.

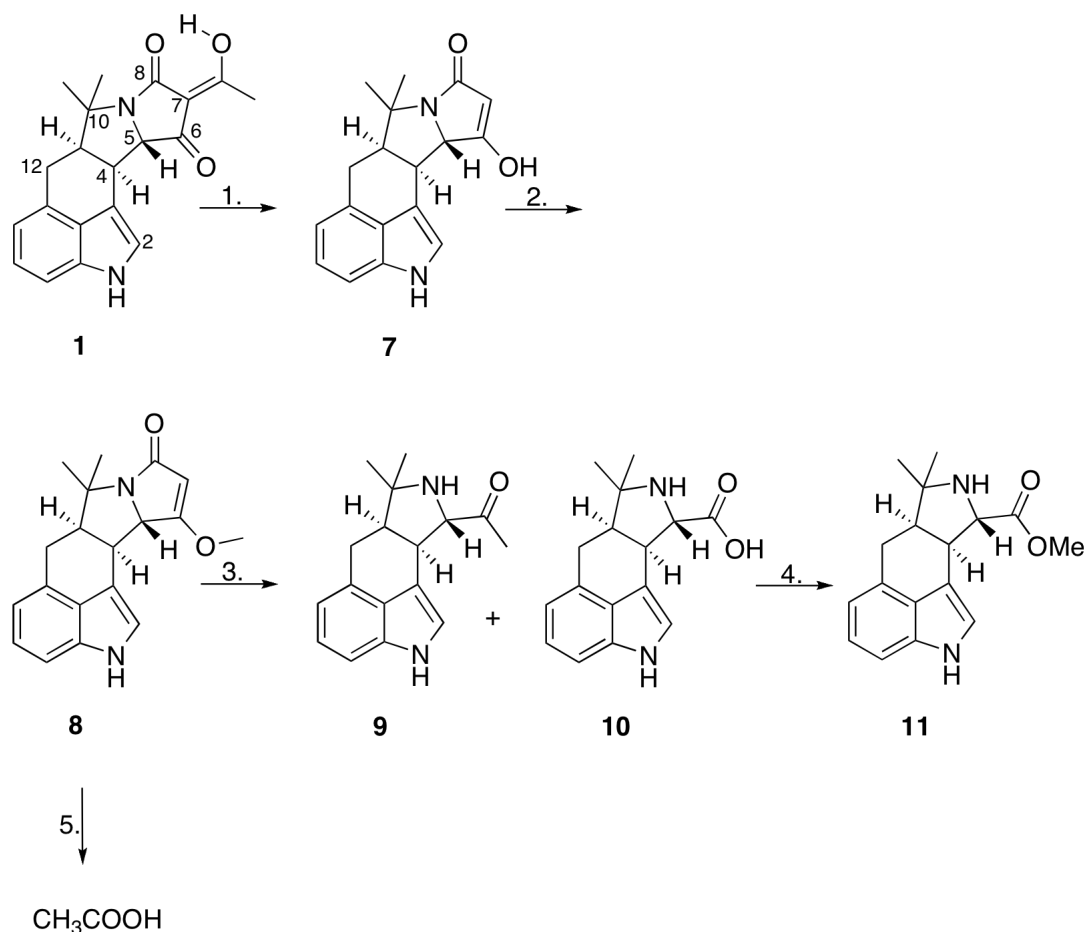
Biosynthetic studies of α -CPA **1** commenced with the postulate that α -CPA **1** was derived from either a molecule of tryptophan and two C₅-units from mevalonic acid or from a molecule of tryptophan, a C₅ unit from mevalonic acid and two molecules of acetic acid.⁶ The latter possibility would be analogous to the biosynthesis of tenuazonic acid **4**, which is biosynthetically derived from *L*-isoleucine **5** and 2 molecules of acetic acid **6**. Displayed in **Scheme 1**.



With this idea in hand, *Penicillium cyclopium* Westling was grown on a shake culture and radioactive labelled [1-¹⁴C] sodium acetate, [2-¹⁴C] mevalonic acid and DL-tryptophan, universally ¹⁴C-labelled in the phenyl ring, was added to separate mediums. 24.7% of the labelled tryptophan was incorporated into the α-CPA **1** isolated; this efficient inclusion was considered as sufficient evidence to deem tryptophan as a precursor to α-CPA **1**. The [1-¹⁴C] sodium acetate derived α-CPA **1** and [2-¹⁴C] mevalonic acid derived α-CPA **1** was degraded by chemical methods. This is depicted in **Scheme 2**.

3

into the *p*-bromophenacyl ester. The acetic acid obtained from the [2-¹⁴C] mevalonate derived α -CPA **1** was inactive whilst the [1-¹⁴C] acetate labelled α -CPA **1** accounted for 35% of the activity of the starting material. This observation indicates C-17 and C-18 are derived from acetic acid.



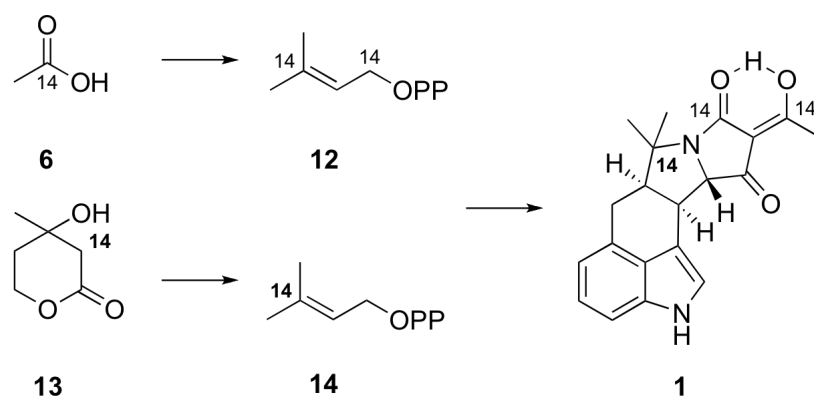
Reagents and Conditions: **1**) 0.1N H₂SO₄, MeOH, reflux, 22hr, **2**) CH₂N₂, Et₂O:MeOH (1:9) **3**) 1N H₂SO₄, MeOH, reflux, 50hr, **4**) SOCl₂, MeOH, reflux, 2hr **5**) 4N Chromic acid:H₂SO₄ (4:1), reflux, 4hr

Scheme 2: Chemical Degradation of α -Cyclopiazonic Acid **1**.

The hydrolysis of tenuazonic acid **4** gives 3-amino-4-methylhexan-2-one **5**, acetic acid **6** and carbon dioxide. These results lead to the expectation that the hydrolysis of **8** synthesised by treating crude **7** with diazomethane would give exclusively **9**. However presence of the methyl enol ether allowed two mechanistic pathways to occur: one resulting in the formation of the expected amino-ketone through hydrolysis

of the amide, decarboxylation and subsequent hydrolysis of the enol ether to the methyl ketone creating **9**, one equivalent of methanol and carbon dioxide, the second by a retro-Claisen condensation generating a *N*-acetyl amino acid which is further hydrolysed to **10** and acetic acid representing C-7 and C-8. Treatment of **10** with thionyl chloride in methanol gave **11**. The acetic acid was partly converted to *p*-bromophenylacyl ester and was degraded by the Schmidt procedure and collected as its barium carbonate. The [2-¹⁴C] mevalonate derived α-CPA **1** was inactive whilst the [1-¹⁴C] acetate labelled α-CPA **1** accounted for 33% of the activity of the starting material. This observation indicates C-7 and C-8 are derived from acetic acid.

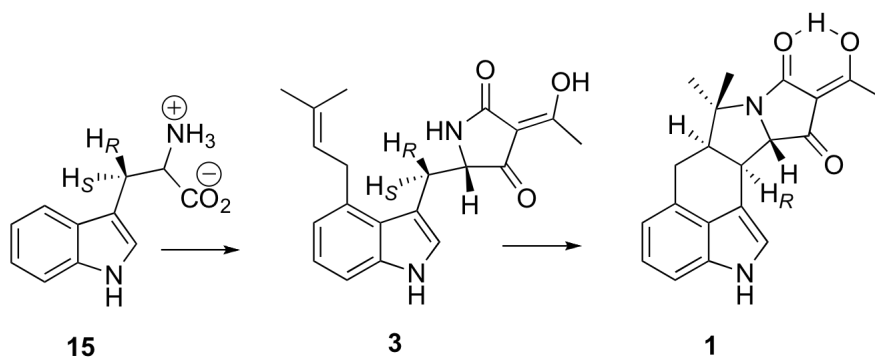
The Kuhn-Roth oxidation with chromium(VI)oxide of **8** yielded acetic acid which was degraded by identical methods. This time the acetic acid obtained from the [2-¹⁴C] mevalonate derived α-CPA **1** accounted for 48% of the activity of the [2-¹⁴C] mevalonate labelled α-CPA **1** whilst the [1-¹⁴C] acetate labelled α-CPA **1** accounted for 15% of the specific molar activity of the starting material. Therefore C-10 and the *geminal* dimethyl group are biosynthetically derived from mevalonic acid. This is summarised in **Scheme 3**.



Scheme 3: Summary of the Biosynthesis α-Cyclopiasonic Acid **1**.

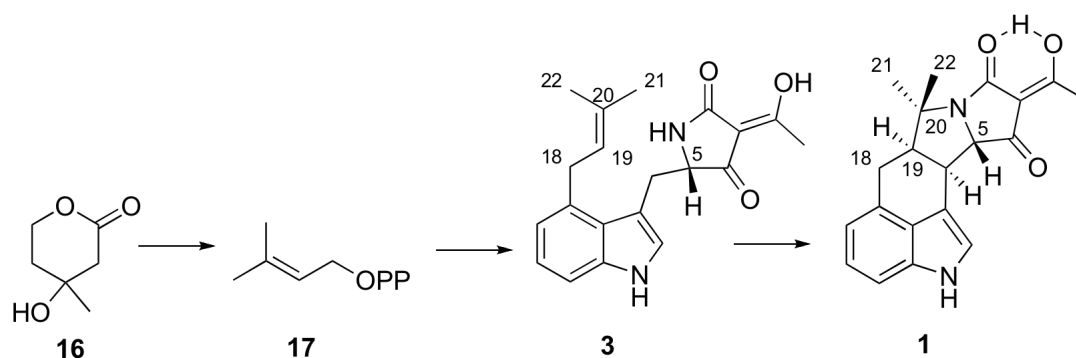
During the investigations it was found that initially β -cyclopiazonic acid **3** concentration rapidly increases when α -CPA **1** is traceable, when formation of **1** increases concentration of **3** falls rapidly. This observation implies that β -cyclopiazonic acid **3** is the direct biological precursor to α -CPA **1**. Culturing labelled β -CPA **3** and adding this to the shake culture tested this proposal. On isolation of α -CPA **1** it contained 67% of the added label and 18% remained in solution. This result verifies that **3** is a direct precursor of **1**.

The stereochemistry of the enzymatic oxidative cyclization of β -CPA **3** to α -CPA **1** was investigated by introduction of (3*R*) and (3*S*)-[3-³H, 3-¹⁴C] tryptophan into cultures of *Penicillium cyclopium* Westling.⁷ The tritium from (3*R*)-[3-³H] tryptophan was retained during conversion into α -CPA **1**, conversely (3*S*)-[3-³H] tryptophan lost all of its tritium. As expected the racemic [3-³H] tryptophan lost half of its tritium. All of the tritiated tryptophans were incorporated into β -CPA **3** confirming the integrity of the methylene group during the preceding steps. These observations show that the *pro-S*-tritium is lost during the final cyclisation indicating that the C-C bond is formed on the opposite side of the molecule to the proton removed.⁸ This is represented in **Scheme 4**.



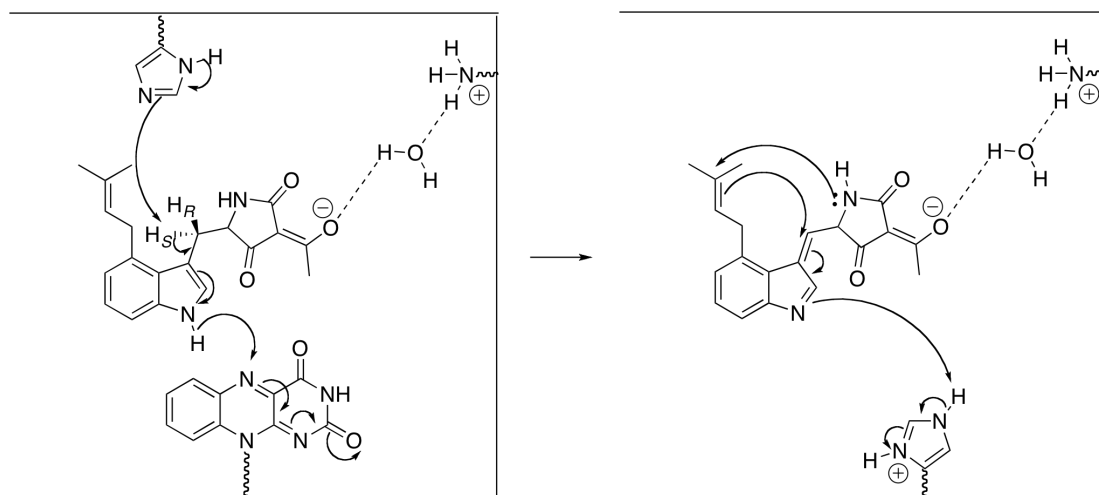
Scheme 4: Stereochemistry of Enzymatic Oxidative Cyclisation of β -CPA **3**.

The stereochemical aspects of the formation of ring D have been investigated by adding stereospecifically labelled [4-³H] mevalonic acid lactone, (3*RS*)-[2-¹⁴C] and (3*R*)-[3-¹⁴C] mevalonic acid lactone to cultures of *Penicillium cyclopium* Westling. Analysis signified the incorporation of the (3*R*)-[3-¹⁴C] mevalonic acid lactone with retention of 4-*pro-R*-hydrogen. Spectroscopic equivalence of the *geminal* methyl group in **1** makes unambiguous assignment impossible. However conversion of α -CPA **1** to *O*-methyl-desacetyl-cyclopiazonic acid **8** allowed for absolute assignment of the dimethyl *geminal* group, it was found that the *Z*-methyl becomes the methyl group at C-22.⁹ This depicted in **Scheme 5**.



Scheme 5: Stereochemistry of Dimethyl *Geminal* Moiety.

A quintet of iso-enzymes called β -cyclopiazonate oxidocyclases is responsible for the cyclisation of β -CPA **3** to α -CPA **1**.¹⁰ The mechanism of the oxidative cyclisation of β -CPA **3** to α -CPA **1** has been extensively investigated by a series of kinetic studies implementing electron acceptors and carriers and has been described as the so-called ‘ping-pong’ mechanism.¹¹ This is delineated below in **Scheme 6**.



Scheme 6: Mechanism of Enzymatic Oxidative Cyclisation.

The mechanism above is however fundamentally incorrect and it would be realistic to relate the 1st step of the oxidative cyclisation to the oxidation of dihydropyridine with dichlorodicyanoquinone. This implies that an imidazole residue is removing the indolic proton and the *pro-S* hydrogen being accepted by the electron acceptor.

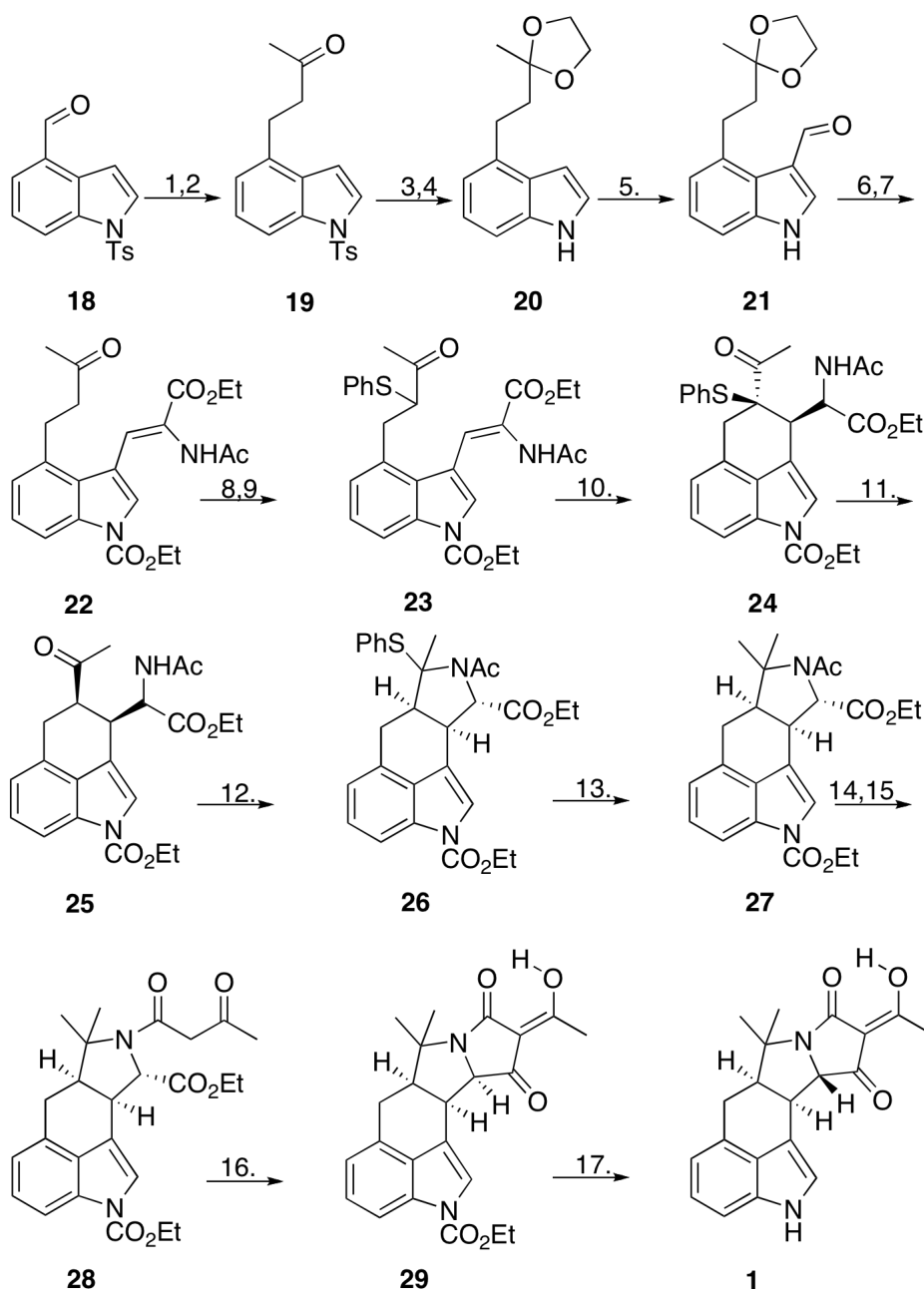
Recently α -CPA **1** has enjoyed a heightened profile since it was discovered that it is a specific inhibitor of Ca^{2+} ATPase, the very origin of its toxicity.¹² Ca^{2+} ATPase is a P-type ATPase, which constitutes of a superfamily of cation transport enzymes, present both in prokaryota and eukaryota, whose members mediate membrane flux of all common biologically relevant cations.¹³ Since α -CPA **1** is a specific inhibitor of the Ca^{2+} ATPase it is regarded as useful biological standard.

1.3 Previous Syntheses

To date there have been three total syntheses of α -CPA **1**, all starting from a suitable 3,4 disubstituted indole. Kozikowski and Greco accomplished the first synthesis in 1984.¹⁴ They took the readily available *N*-tosyl derivative of indole-4-carboxyaldehyde **18** and transformed it to **19** in 89% yield using a Wittig reaction followed by palladium catalysed hydrogenation. The ketone moiety of 4-(1-tosyl-1H-

indol-4-yl)butan-2-one **19** was protected as its ethylene ketal using ethane-1,2-diol under acidic conditions and subsequent deprotection of the N-tosyl group gave **20** in 92% yield. Under standard Vilsmeier protocol position 2 of the indole was formylated providing **21**, followed by the use of 2-acetamido-3-methoxy-3-oxopropanoic acid, the amidoacrylate group was efficiently installed and subsequent protection of the indolic nitrogen with methyl chloroformate gave **22** in overall yield of 46% from **20**. Deprotection of the ketal followed by formation of the thermodynamic silyl enol ether and reaction with phenylsulphenyl chloride afforded **23** in 54% yield. Intramolecular Michael addition promoted by DBU formed the central carbocyclic ring of **24** in 55% yield. On conversion of **24** to **25** an interesting Raney Nickel induced desulfurization occurs leading almost exclusively to the cis compound **25** in 72% yield. This reaction is contrathermodynamic in nature since stirring of **25** with DBU leads exclusively to the trans isomer. Closure of ring **D** was affected by use of thiophenol with magnesium(II)triflate, creating α -phenylthioamide intermediate **26** in 80% yield. A survey of a multitude of organometallic reagents found that dimethylzinc in chloroform was the sole reagent capable of replacing the thio group and installing the geminal dimethyl moiety, converting **26** to **27** in 73% yield. Deprotection of the acetamide **27** with triethyloxonium tetrafluoroborate in dichloromethane occurred in 79% yield followed by reaction with diketene afforded acetoacetamide **28** in 80%. Base catalysed cyclisation of **28** to the tetramic acid residue with sodium methoxide surprisingly gave iso α -CPA **29**. Epimerization with triethylamine in chloroform gave α -CPA **1**:iso α -CPA **29**, 5:2.

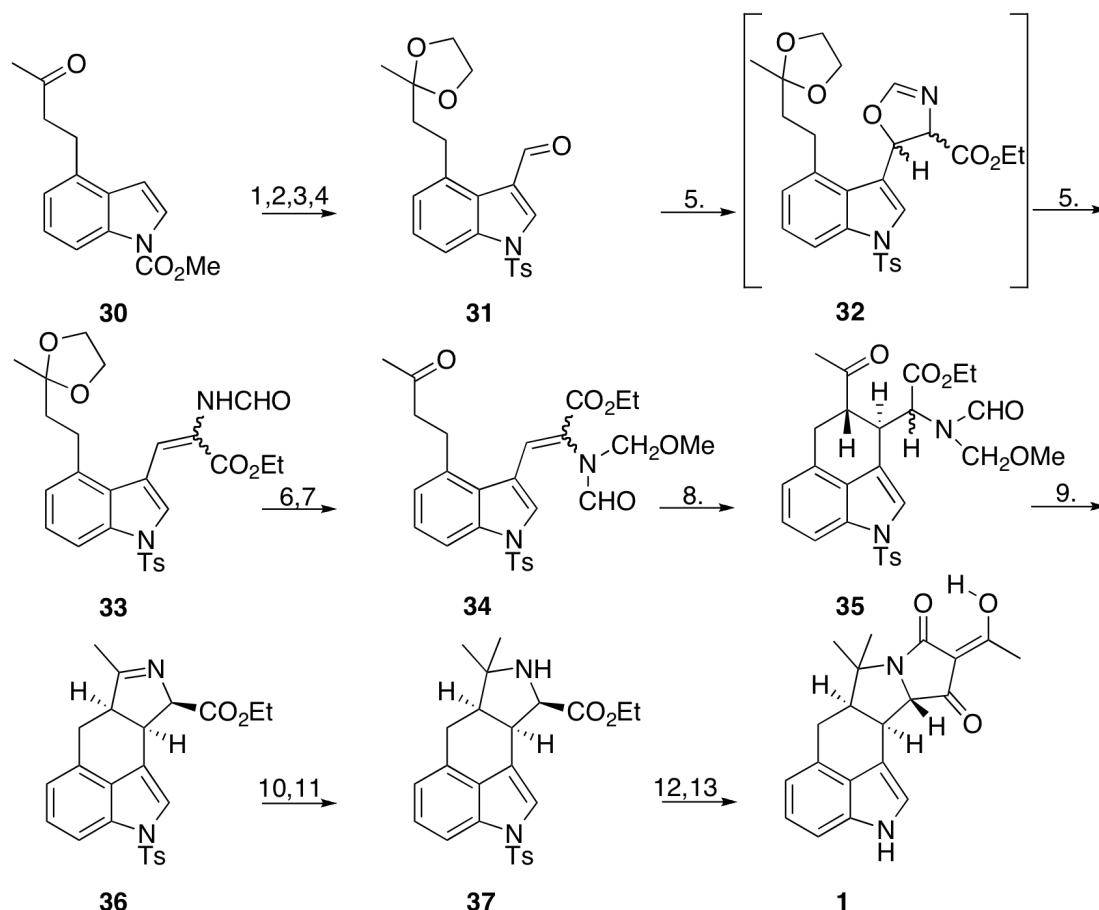
Kozikowski and Greco completed the first synthesis of α -CPA **1** in 16 steps from 1-tosyl-1H-indole-4-carbaldehyde **18** in an overall yield of 2.1 %. This is shown below in **Scheme 7**.



Reagents and Conditions: 1) $\text{CH}_3\text{COCH}=\text{PPh}_3$, THF, 95%, 2) H_2 , Pd/C, MeOH-THF, 94%, 3) $\text{HO}(\text{CH}_2)_2\text{OH}$, *p*-TsOH, PhH, 99%, 4) 4N KOH, MeOH, 93%, 5) POCl_3 , DMF, then NaOH, 62%, 6) $\text{AcNHCH}(\text{CO}_2\text{Et})\text{CO}_2\text{H}$, Ac_2O , pyr, 78%, 7) ClCO_2Et , Et_3N , 95%, 8) 10% HCl, THF, 98%, 9) MeSiI, $\text{HN}(\text{SiMe}_3)_2$, then PhSCl, 55%, 10) DBU, *t*-BuOH, reflux, 60%, 11) H_2 , Raney Ni, 72%, 12) PhSH, $\text{Mg}(\text{OTf})_2$, 80%, 13) Me_2Zn , CH_3Cl , 73%, 14) Et_3OBF_4 , Na_2CO_3 , THF, CH_2Cl_2 , 79%, 15) Diketene, EtOH, 80%, 16) NaOMe, MeOH, PhH, 17) Et_3N , CH_3Cl , 100°C

Scheme 7: Kozikowski and Greco's Synthesis of α -CPA **1**.

Muratake and Natsume completed the second synthesis in 1985.¹⁵ This is outlined in **Scheme 8**.

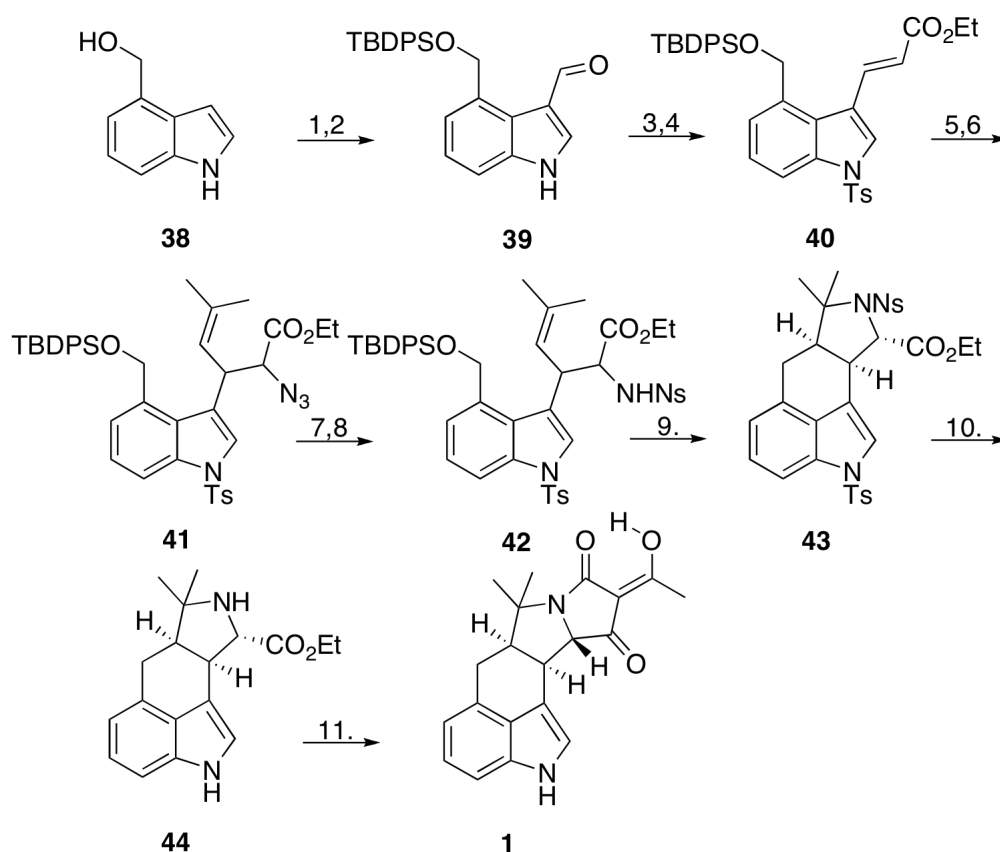


Reagents and Conditions: **1)** HO(CH₂)₂OH, *p*TsOH, 80°C, 1hr, **2)** 2% KOH, MeOH:H₂O:DME (3:1:1), rt, 1.5hr, 91% (2 steps), POCl₃, DMF, Et₂O, 0°C to rt, 30min, 78%, **4)** *p*TsCl, Et₃N, CH₂Cl₂, rt, 1hr, 93%, **5)** ethyl isocyanoacetate, ^{*t*}BuOK, THF, -81 to 20°C, 1hr, then ^{*t*}BuOK, THF, -83 to 20°C, 30 min, 84% **6)** 50% NaH, DMF, 0°C, 20min; then ClCH₂OMe, THF, -83 to -20°C, 30min, 61% **7)** acetone, *p*TsOH, rt, 14hr, 100%, **8)** DBU, PhH, 80°C, 6hr, 52% **9)** 1N HCl, EtOH, H₂O, reflux, 3hr, 66%, **10)** BF₃·Et₂O, THF, 0°C, 5min then MeLi, Et₂O, -80 to 65°C, 45min, 40%, **11)** 10% KOH in EtOH:H₂O (3:1), reflux, 3hr then *p*TsOEt, EtOH, reflux, 14hr, 52%, **12)** diketene, CH₂Cl₂, reflux, 2hr, 81%, **13)** Et₃N, PhH, reflux, 15hr, 40%

Scheme 8: Muratake and Natsume's Synthesis of α-CPA **1**.

In an almost identical initial sequence compound **30** was protected as its ethylene ketal, the methyl formate group was removed with potassium hydroxide in a water, methanol and dimethoxyethane to permit the subsequent Vilsmeier reaction. The tosyl group was then reinstalled giving **31** in 66% over 4 steps. Deprotonation of ethyl

isocyanoacetate with potassium *tert*-butoxide gave oxazolidine derivative **32**, a second deprotonation cleaved the oxazolidine forming **33** in 68% yield. This is an interesting alternative to forming the amidoacrylate moiety of **33** compared with the first synthesis. Protection of the nitrogen functionality with chloro(methoxy)methane in THF followed by removal of the ethylene ketal generated **34** in 84% yield. An intramolecular Michael reaction, initiated by treatment with DBU was utilised to close the central ring forming **35** in 52% yield. In one synthetic operation both the methoxy methyl group and the aminal were hydrolysed, followed by closure of ring **D** to afford ketimine derivative **36** in 66%. Fortunately epimerization at C-8 occurred during this step. Installation of the geminal dimethyl group was achieved by initially complexing ketimine derivative with $\text{BF}_3 \cdot \text{OEt}_2$ followed by addition of methyl lithium, subsequent deprotection of the indolic nitrogen yielded **37** in 20% yield. The tetramic acid residue was installed using the method of Kozikowski and Greco;¹⁴ addition of the pyrrolidine to diketene followed by a Dieckman condensation furnished iso α -CPA **29** followed by isomerisation yielded α -CPA **1** in an overall yield of 1.6% over 13 steps.



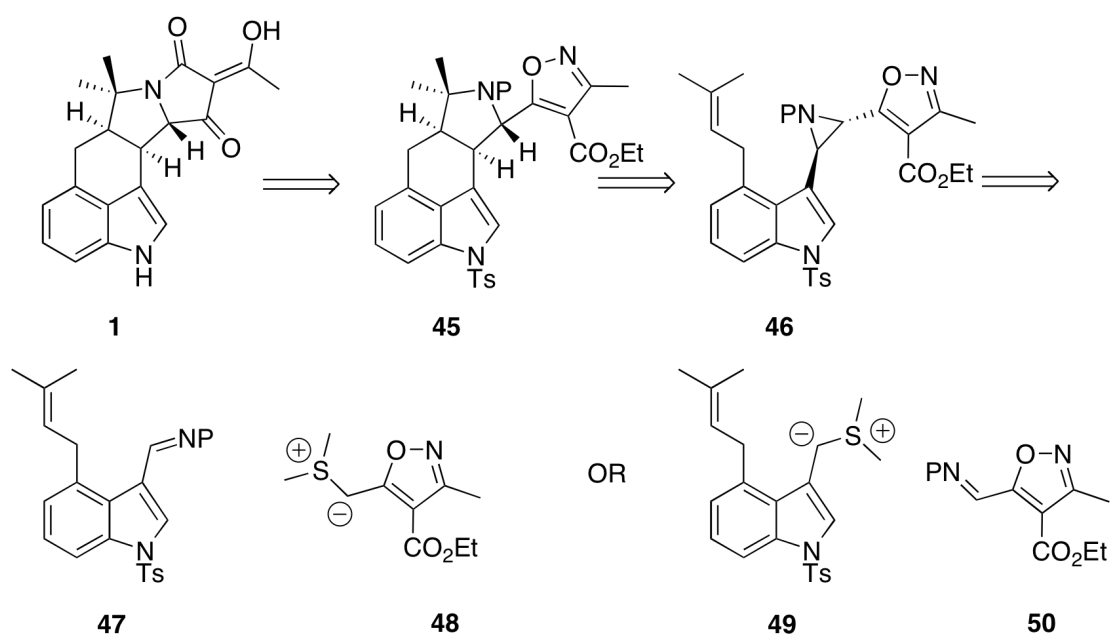
Reagents and Conditions: **1**) TBDPSiCl, imidazole, THF, 20°C, 16hr, 95%, **2**) POCl₃, DMF, pyridine, 0 to 35°C, 45min, then 0.5N NaOH, reflux, 2min, 82%, **3**) TsCl, Et₃N, DMAP, CH₂Cl₂, 20°C, 16hr, 85%, **4**) (EtO)₂POCH₂CO₂Et, LiCl, MeCN, DBN, 20°C, 15 min then add **39**, 20°C, 2hr, 62%, **5**) Me₂CCHMgBr, PhSCu, -40 to 0°C, 1hr then add **41**, -40 to 20°C, 30 min, 53%, **6**) KHMDS, THF, trisyl azide, -78°C, 5min, 62%, **7**) PPh₃, H₂O, THF, 60°C, 6hr, **8**) pNO₂C₆H₄SO₂Cl, py, DMAP, CHCl₃, 20°C, 16hr, 43% 2steps, **9**) TFOH, CHCl₃, 20°C, 1hr, 74%, **10**) LiO₂CCH₂SLi, 82%, **11**) diketene, CH₂Cl₂, reflux, 2hr, 89%

Scheme 9: Knight and Haskins' Synthesis of α -CPA **1**

Knight and Haskins completed the third and final synthesis of α -CPA **1** featuring a novel intramolecular cationic cascade.¹⁶ As with all previous syntheses a C-4 substituted indole derivative was the starting point. In this case indole-4-methanol **38** was protected at oxygen with complete chemoselectivity using tert-butylchlorodiphenylsilane with imidazole in THF. Formylation under standard Vilsmeier conditions formed **39** in 78% yield. Indolic protection with tosyl chloride followed by homologation under Wadsworths-Emmons conditions gave α,β unsaturated ethyl ester **40**. Addition of (2-methylprop-1-enyl)magnesium bromide

in the presence of phenylthiocopper gave exclusively the 1,4 adduct in 53% yield. Deprotonation with LiHMDS and subsequent addition of trisyl azide gave **41** in 62% yield. Reduction of azide **41** with triphenylphosphine and water in THF followed by nosylation gave cationic cascade precursor **42** in 43% over two steps. Treatment of **42** with triflic acid in chloroform at room temperature yielded tetracycle **43** in 74% yield, impressive for such an elaborate step. Global deprotection with thioglycolate proceeded in 82% yield giving common intermediate **44**. The synthesis was completed with the addition of diketene in methylene dichloride yielding 89% of **1**. Summarised in **Scheme 9**.

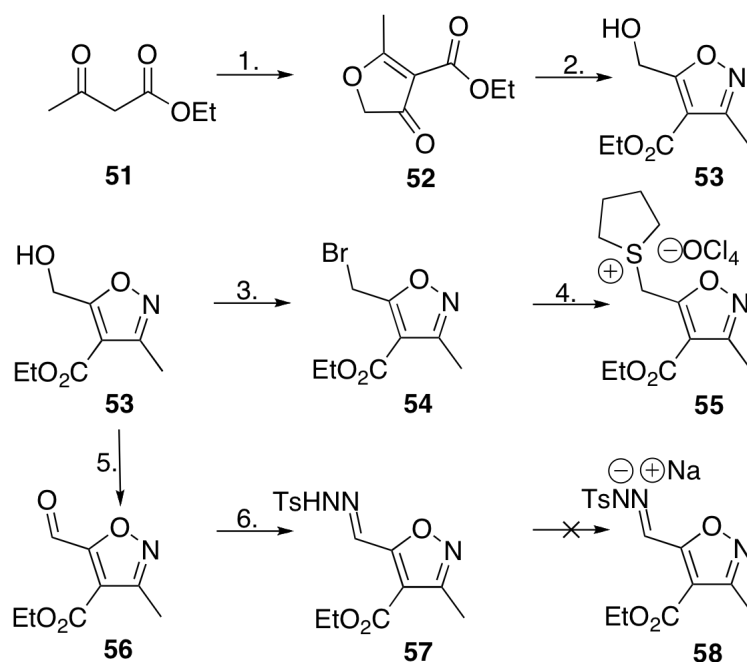
Aggarwal and Co-workers have recently published a fourth approach to α -CPA **1**.¹⁷ Contrasting all previous syntheses the tetramic acid moiety of **1** was simplified to isoxazole **45**. This disconnection is based on literature precedent for the hydrogenolysis of isoxazoles.¹⁸⁻²¹ A biomimetic approach has for the installation of the two non-indolic rings has been proposed based on the ‘ping-pong’ mechanism.¹¹ Two complimentary routes to aziridine **46**, based on previous work from the Aggarwal group,^{22, 23} have been considered via either indolic imine **47** and isoxazole sulfonium ylide **48** or iminic isoxazole **49** and indolic sulfonium ylide **50**. This is summarised in **Scheme 10**.



Scheme 10: Aggarwal's Retrosynthetic Analysis of α -CPA **1**

At the present time the synthesis of isoxazole partners **48** and **50** has been achieved.

After intense investigation the synthetic sequence displayed below in **Scheme 11** was found to be the optimal route to such species.



Reagents and Conditions: 1) $\text{Mg}(\text{OEt})_2$, PhH, rt, 1hr then MeCN, α -chloroacetyl chloride, -10°C to rt, 2hr, 2) NaOAc, $\text{NH}_2\text{OH}\cdot\text{HCl}$, EtOH, 80°C , 2hr, 79% over 2 steps, 3) DMF, PBr_3 , PhMe, 110°C , 1hr, 100%, 4) tetrahydrothiophene, NaOCl_4 , acetone, rt, 2days, 91%, 5) PCC, CH_2Cl_2 , rt, 2 weeks, 82%, 6) TsNHNH_2 , MeOH, 0°C , 1hr, 66%

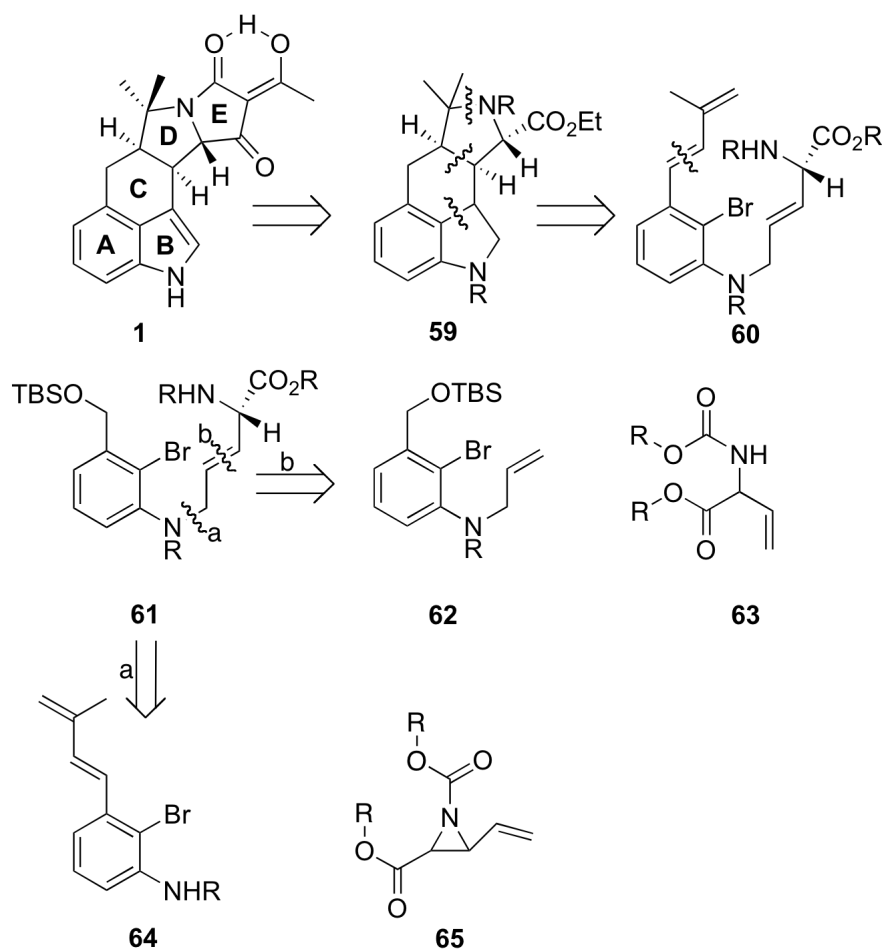
Scheme 11: Synthesis of Isoxazole Partner

Implementing a modified procedure to the approach published by Gelin and co-workers,²⁴ alcohol **53** was synthesised by addition of chloro acetyl chloride in acetonitrile to a complex of ethyl aceto acetate **51** and magnesium(II)ethoxide in benzene. Treatment of crude **52** with hydroxylamine hydrochloride and sodium acetate in ethanol furnished **53** in 79% yield from ethyl aceto acetate **51**. Bromide **54** was obtained in quantitative yield by treatment of alcohol **53** with an equimolar amount of phosphorus tribromide and DMF in refluxing toluene. The best possible conditions for the displacement was the treatment of bromide **54** with tetrahydrothiophene and sodium perchlorate in acetone for two days at room temperature affording salt **55** in 91% yield. The oxidation of alcohol **53** was accomplished by stirring **53** in dichloromethane with PCC for two weeks yielding 82% of aldehyde **56**. Tosylhydrazone **57** was readily available in 76% yield by reaction of tosylhydrazide

with aldehyde **56**. Attempts to isolate **58** were unsuccessful, freshly prepared sodium methoxide affected the deprotonation of **57** however upon even low temperature work-up decomposition to the diazo compound occurred. This observation is not problematic since the catalytic aziridination can occur direct from the diazo compound or *via* in situ deprotonation. Aggarwal and co-workers plan to obviously synthesise the indole partner and finish the synthesis.

1.4 Retrosynthetic Analysis

On inspection it was conceived that α -CPA **1** could be synthesised from a radical cascade process. Similarly to all previous total syntheses of α -CPA **1** the teramic acid moiety will be installed in an identical fashion. Retrosynthetic analysis revealed that the ABC ring system of simplified species **59** could be closed in one step from acyclic intermediate **60**. Tin mediated homolytic cleavage of the carbon-bromine bond forming an aryl radical, followed by a tandem 5-*exo-trig*, 6-*endo-trig* cascade sequence would provide a suitable intermediate that when treated with acid would close ring **D** *via* a stable tertiary cation and furnish the tetracyclic core of α -CPA **1**. The triene moiety of **60** could be simplified to silyl protected derivative **61**. Two different approaches were envisaged for the synthesis of the amino acid side chain of **61**. In disconnection b: it is postulated that an olefin cross metathesis route could yield **61**; protected allyl amine **62** with vinyl glycine derivative **63** with the aid of a suitable Grubbs alkene metathesis catalyst would yield **61**. Alternatively an enantiopure vinyl aziridine **65** could be opened 1,4 by diene **64**.



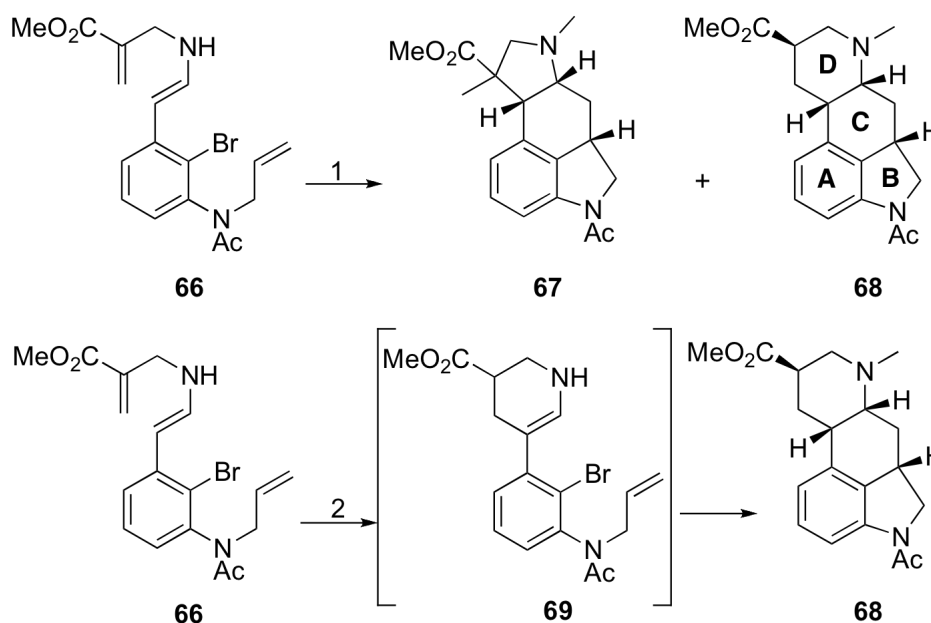
Scheme 12: Retrosynthesis of α -CPA **1**.

The synthesis of the 1,2,3 trisubstituted aniline **62** has been previously described by Parsons *et al.* in their synthesis of lysergic acid and derivatives.^{25, 26, 27} These papers also describe 5-*exo-trig*, 6-*endo-trig* radical cascades.

1.5 Radical Cascades in Natural Product Synthesis

The structural framework of lysergic acid was synthesised from acyclic intermediate **66** by slow addition of a solution of tributyltin hydride and AIBN in toluene to a boiling solution of enamine **66**. Two tetracyclic products were formed **67** and **68** in 73% yield and in a ratio of 1:2. After the initial previously unprecedented 5-*exo-trig*, 6-*endo-trig* bicyclisation, two competing modes of cyclisation were possible, the major product **68** from the 6-*endo-trig* mode and minor **67** from the 5-*exo-trig* mode.

Heating precursor **66** for 5 hours in toluene to cause closure of ring **D** circumvented this problem then addition of AIBN and Bu₃SnH formed **68** exclusively in 74% yield.



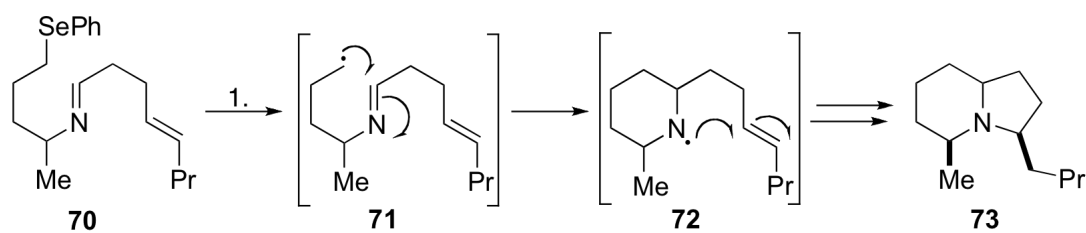
Reagents and Conditions: 1) Bu₃SnH, AIBN, PhMe, 24hr, reflux, 74%, 1:2, **67:68**, 2) PhMe, 5hr, reflux then Bu₃SnH, AIBN, PhMe, 24hr, reflux, 74%

Scheme 13: Parsons *et al.* Synthesis of Lysergic Acid Derivatives.

Since the discovery of the stable triphenylmethyl radical by Gomberg in 1900,^{28, 29, 30} the ability of the organic chemist to manipulate the reactivity of radicals has increased to such an extent that controlled chain reactions, aided by the development of a diversity of new reagents and synthetic methods, have been implemented to construct complex molecular architectures in one step from acyclic precursors, this being exemplified by the ubiquity of publications in the literature. The forthcoming pages are merely a representation of the possibilities of radical cascade reactions.

Bowman *et al.* have demonstrated that imines are efficient radical acceptors in their synthesis of a variety of nitrogen heterocycles.³¹ An example is Monomorpine **73**, where acyclic phenyl selenide precursor **70** was subjected to tributyltin hydride in toluene with a catalytic amount of AIBN. A reactive primary radical was formed

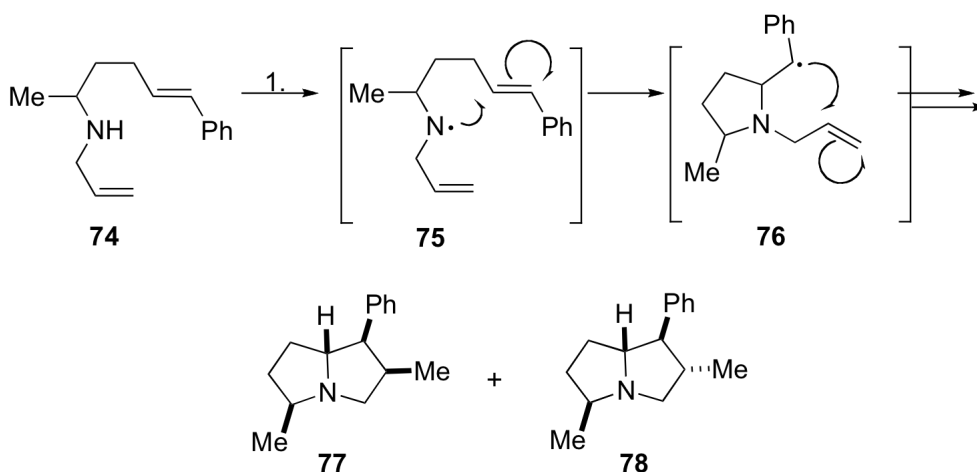
which cyclised in a 6-*endo-trig* fashion creating high energy nitrogen based radical species **72** that spontaneously cyclised in a 5-*exo-trig* mode to form monomorphine **73**.



Reagents and Conditions: 1) TBTH, AIBN, PhMe, reflux, 18hr, 19%

Scheme 14: Synthesis of Monomorphine **73**.

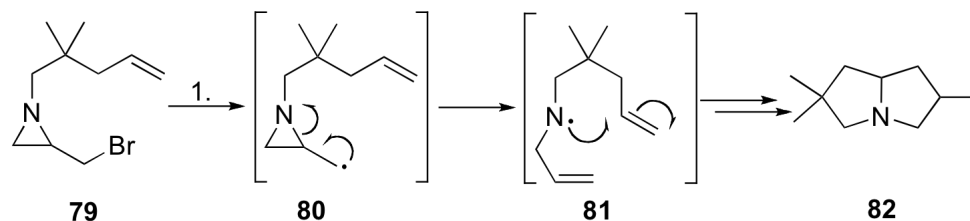
Senboku *et al* demonstrated use of a differing radical cascade sequence towards indolizidines.³² In one pot allyl amine derivative **74** was exclusively *N*-chlorinated on treatment with *N*-chlorosuccinimide in toluene for thirty minutes, subsequent addition of AIBN and TBTH formed a highly reactive nitrogen bound radical species **75** which cyclised in a 5-*exo-trig* fashion onto the styrene moiety forming benzylic radical **76** that reacted in 5-*exo-trig* mode to close the indolizidine ring structure. Compounds **77** and **78** were formed in 82% yield in a ratio of 3:5.



Reagents and Conditions: 1) NCS, toluene, 30 mins, rt, then AIBN, TBTH, 7hr, reflux, 82%, 3:5 **77**:**78**

Scheme 15: Radical Approach to Indolizidines.

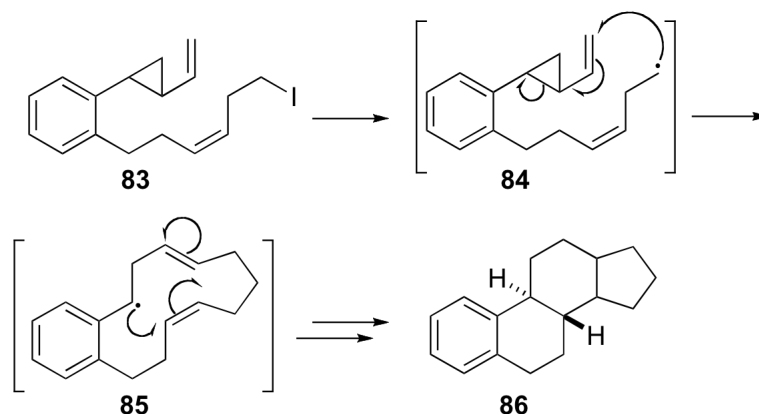
Readily available 2-(bromomethyl) aziridine derivatives were employed in a fragmentation, 5-*exo-trig*, 5-*exo-trig* sequence to yield indolizidine structures by De Kimpe and Co-Workers.³³



Reagents and Conditions: 1) TBTH, AIBN, PhH, 80°C, 4hr, 62%

Scheme 16: Alternative Radical Approach to Indolizidines.

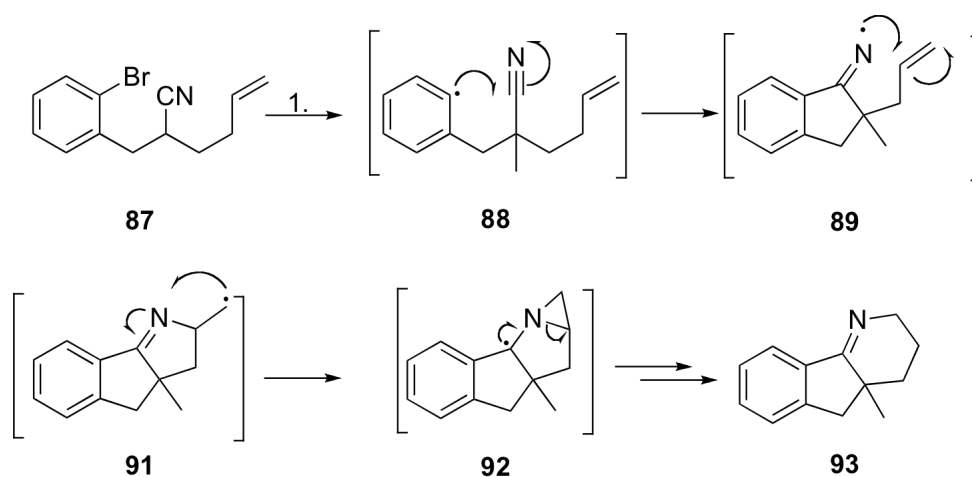
Pattenden and Wiedenau have demonstrated the use of cyclopropanes in radical cascades towards the cortical steroid architecture.³⁴ Iodide **83** was treated (tristrimethylsilyl)silane and AIBN in benzene affording **86** in 16% yield.



Reagents and Conditions: 1) (Me₃Si)₃SiH, AIBN, PhH, 14hr, syringe pump, 16%

Scheme 17: Radical Approach to the Cortical Steroid Architecture

Bowman *et al.* have publicized that cyanide groups are also radical acceptors.³⁵ On exposure of **87** to tributyltinhydride and a catalytic amount of AIBN, aryl radical **88** was formed; this reacted in a 5-*exo-trig* mode onto the nitrile group creating iminyl radical, **89**, that cyclised in an identical manner onto the allyl group forming a reactive primary radical. Subsequent formation of aziridine **92** followed by fragmentation gave **93** in 34% yield.

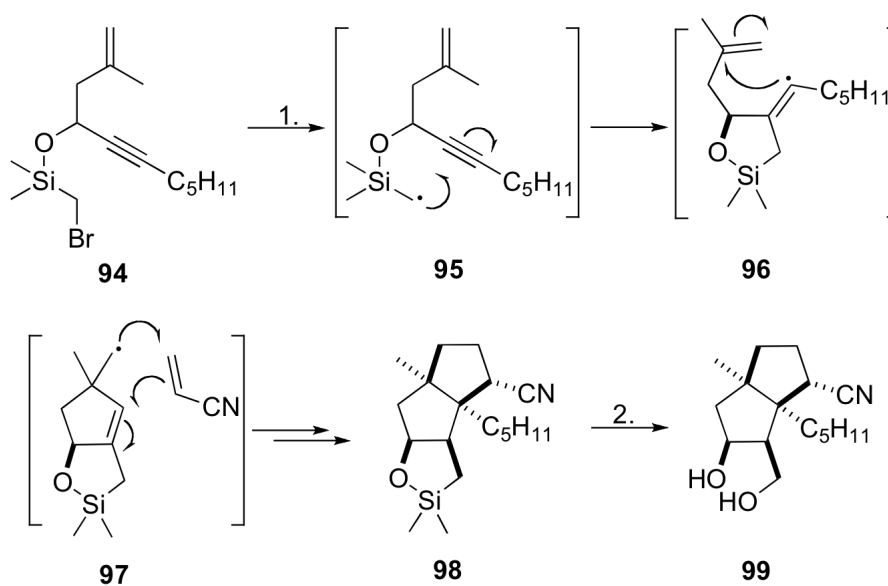


Reagents and Conditions: 1) TBTH, AIBN, toluene, 3hr, syringe pump, 34%

Scheme 18: Cyanide as a Radical Acceptor.

An elegant utilization of a silicon tether in combination with a domino intra-intermolecular cascade sequence yielding 5,5 fused ring systems in moderate yields.³⁶

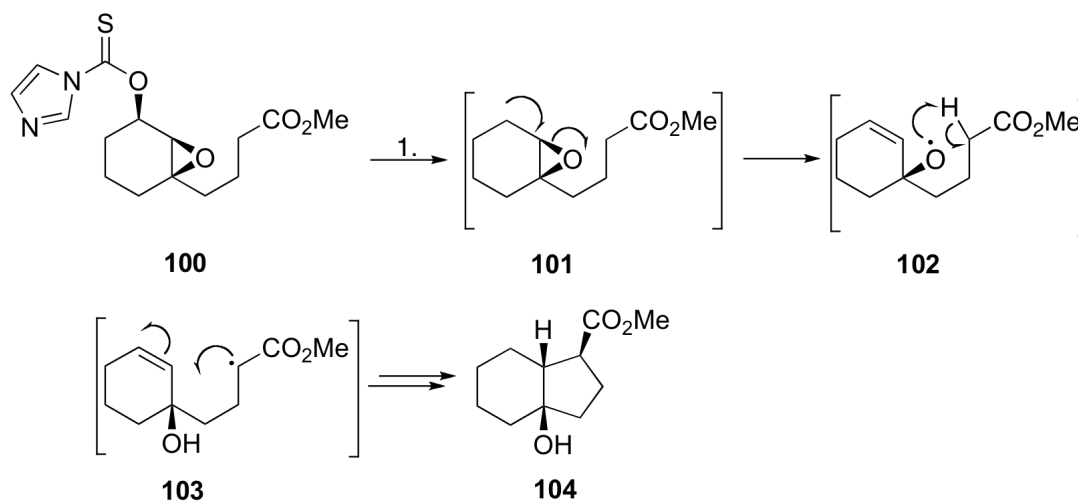
This is displayed below in **Scheme 19**.



Reagents and Conditions: 1) Ph_3SnH , ACN, AIBN, 51%

Scheme 19: A Domino Intra-Intermolecular Cascade

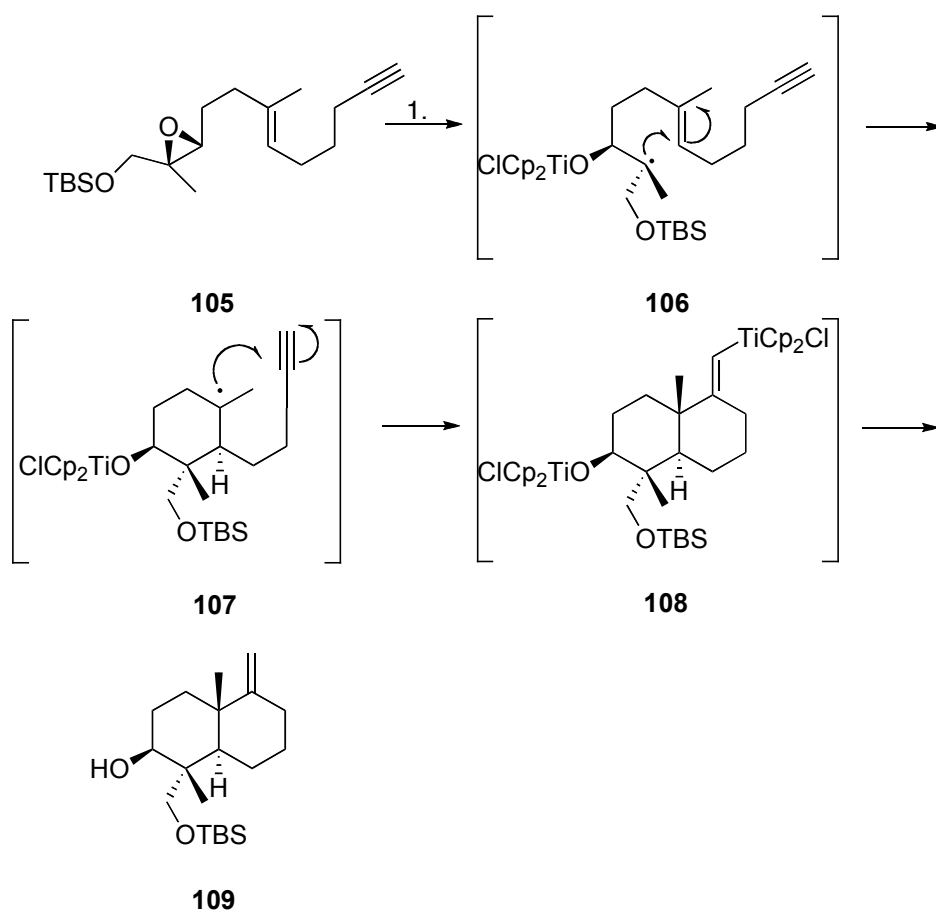
Rawal and co-workers exploited the strained nature of epoxides and reactivity of alkoxy radicals in their epoxide fragmentation, H-abstraction, 5-*exo-trig* cyclisation sequence that transformed **100** to **104**.³⁷



Reagents and Conditions: 1) TBTH, AIBN, PhMe, reflux, 69%

Scheme 20: Epoxides and Alkoxy Radicals

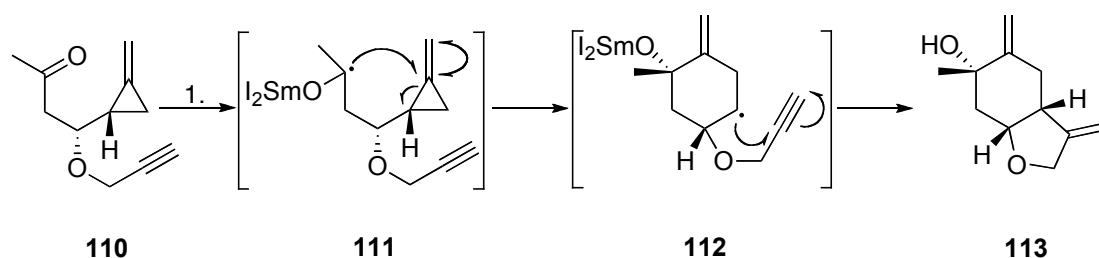
Titanocene mediated reductive epoxide opening has been utilised in a remarkable 6-*endo-trig*, 6-*exo-dig* tandem sequence towards the synthesis of Smenospondiol. A key requirement for this process was the use of a mixture of benzene and THF (5:1) at reflux.^{38 39} This is displayed in **Scheme 21**.



Reagents and Conditions: 1) 2eq. Cp_2TiCl_2 , PhH:THF, 5:1, 60°C, 77%

Scheme 21: Titanocene as a Radical Initiator.

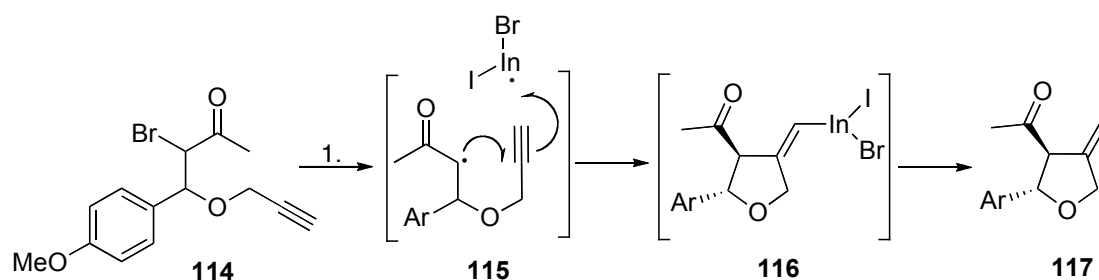
Samarium(II)iodide has been employed as a selective and mild reductant in many radical and anionic cascades. Kilburn *et al.* have utilised this reagent in a synthesis of paconilactone B; their route features a cascade sequence involving a methylene cyclopropane group.⁴⁰ Treatment of ketone **110** with samarium diiodide in the presence of HMPA and ^tBuOH results in single electron reduction of **110** to give ketyl radical **111** that spontaneously cyclises in a 5-*exo-trig* fashion to give an unstable cyclopropyl carbinyl radical that undergoes facile ring expansion to give homoallyl radical **112**, subsequent 5-*exo-dig* cyclisation furnishes **113** in 63% yield as 10:1 mixture of diastereoisomers at the hydroxyl substituted carbon.



*Reagents and Conditions: 1) SmI₂, HMPA, *t*BuOH, THF, 0 to 25°C*

Scheme 22: Samarium(II)Iodide Initiated Cascade.

The use of indium(I)iodide to generate radicals has been reported by Ranu and Mandal.⁴¹ Although yet to be utilized in a domino reaction their observation is worthy of note. It was found that sonication of intermediate **114** at room temperature was the only method of inducing cyclisation to **117**. Reflux created a complex mixture and no reaction occurred at room temperature. Acetonitrile as a solvent was deemed essential as no reaction occurred in less polar solvents. The addition of radical quenchers such as TEMPO and *p*-benzoquinone arrested the cyclisation process. One downfall of the process was that an aryl group and an electron withdrawing group had to be adjacent to the latent radical. The mechanism is summarised below.

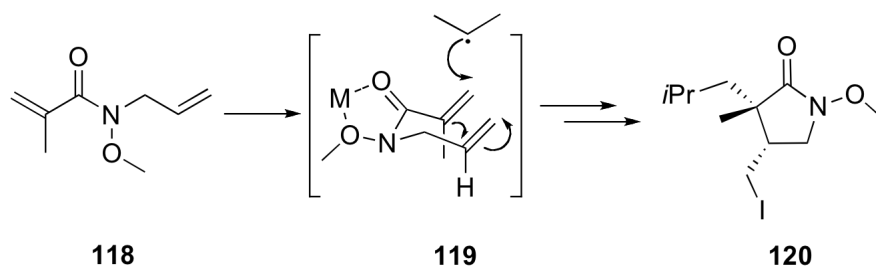


Reagents and Conditions: 1) InI, MeCN, sonication, 68%

Scheme 23: Indium(I)Iodide as a Radical Initiator.

An enantioselective cascade has been utilised by Miyabe *et al.* for the synthesis of highly functionalised cyclic amides.⁴² After intense investigation it was found that the optimal conditions were the use of zinc(II)triflate as a Lewis acid, which was essential since the reaction ceased without it, oxazole as a chiral ligand and initiation with

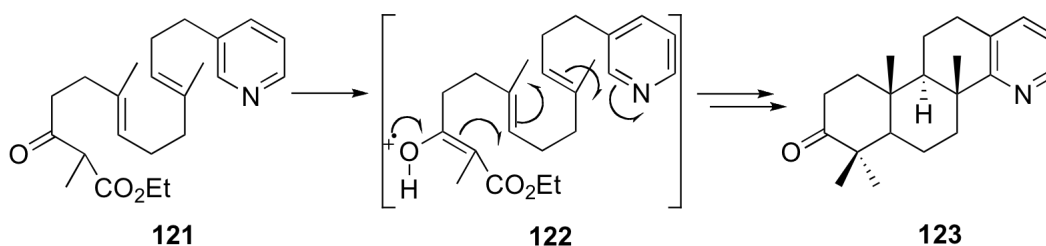
triethylborane. Once **118** is held in the fixed transition state **119** by a chiral Lewis acid, attack of the isopropenyl radical proceeds stereospecifically, and is followed by halogen abstraction to yield **120** in 75% yield, 82% *ee*. This is a remarkable transformation forming 3 bonds, a quaternary centre and two stereogenic centres through an inter-intra-inter molecular cascade.



Reagents and Conditions: Chiral Ligand, $\text{Zn}(\text{OTf})_2$, *i*PrI, Et_3B , CH_2Cl_2 , -78°C , 75%, 82% *ee*

Scheme 24: An Inter-Intra Enantioselective Cascade.

Gonzalez and Molina-Navarro described the use of an intramolecular Minisci-type reaction in an approach to Spongidines.⁴³ Under acidic conditions, **121** exists in solution with a significant concentration of its enol tautomer. Manganese(III)acetate abstracts an electron from oxygen, to form alkoxy radical cation **122**. A triple radical cyclisation ensues in 6-*endo-trig*, 6-*endo-trig*, 6-*exo-trig* fashion, followed by rearomatisation yielding **123** in 40% yield.



Reagents and Conditions: 1) $\text{Mn}(\text{OAc})_3$, AcOH , 40%

Scheme 25: Manganese(III)Acetate as a Radical Initiator.

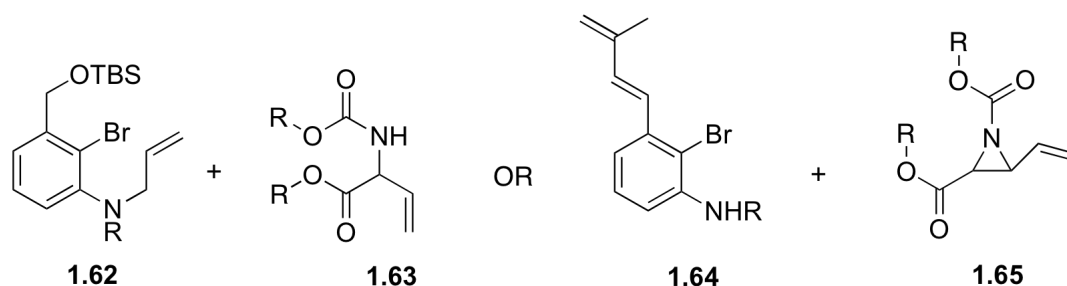
The scope and diversity of radical cascades has been demonstrated. Halides, selenyl derivatives, xanthates, carbonyl groups and epoxides can all be used as latent radicals. Apart from the widely used tributyltinhydride and AIBN system other radical initiators

such as tris(trimethylsilyl)silane, TiCp_2Cl_2 , triethylborane, indium iodide, samarium(II)iodide and manganese(III)acetate have all been successfully employed. A broad range of functional groups including alkenes, alkynes, imines, nitriles, aziridines, epoxides, aromatic heterocycles and cyclopropanes all accept radicals, many reacting further in cascade or domino sequences.

Tandem radical reactions exemplify the elegance of organic synthesis in the 21st century, from the initial stages of designing a synthetic sequence, through theory and imagination, to the execution in a laboratory.

Results and Discussion

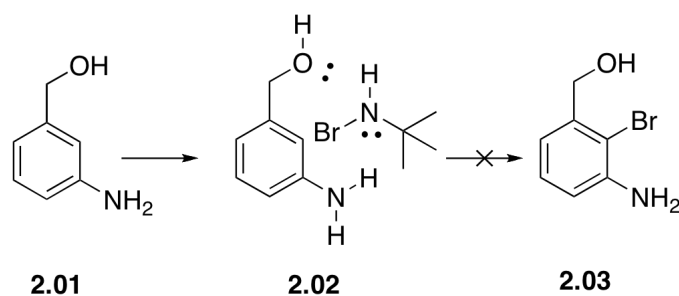
Retrosynthetic analysis of α -CPA **1** has led to two strategies for the construction of the amino side chain either: a cross metathesis between allyl amine **1.62** and protected vinyl glycine **1.63** or a nucleophilic 1,4 addition of diene **1.64** onto vinyl aziridine derivative **1.65**.



Scheme 26: Key Intermediates of Retrosynthetic Analysis

On reviewing the literature the initial plan was to implement the cross metathesis route first since vinyl glycine derivatives have been previously used as partners in cross metathesis,^{44 45, 46, 47,} and the synthesis of enantiopure vinyl glycine has been published.⁴⁸

1,2,3-trisubstituted aromatic compounds are not trivial molecules to synthesise. The aromatic precursor **1.62** has formerly been synthesised by Parsons *et al.* in their synthesis of lysergic acid,^{25, 26} however it requires the use of the toxic mercuric acetate so an alternative strategy was investigated. Pearson *et al.* have described hydrogen bonding induced regioselective bromination of phenols.⁴⁹ Premixing bromine with *tert*-butyl amine in toluene at -70°C, followed by slow addition of phenol, gave exclusively 2-bromophenol in 60% yield. This method has been applied to 2-methoxyphenol obtaining 2-bromo-6-methoxyphenol in 87% yield.^{50 51} The plan was to extend this idea to aniline derivative **2.01**, in the hope that chelation through a double hydrogen bonded intermediate **2.02**, followed by electrophilic aromatic substitution would give compound **2.03**.



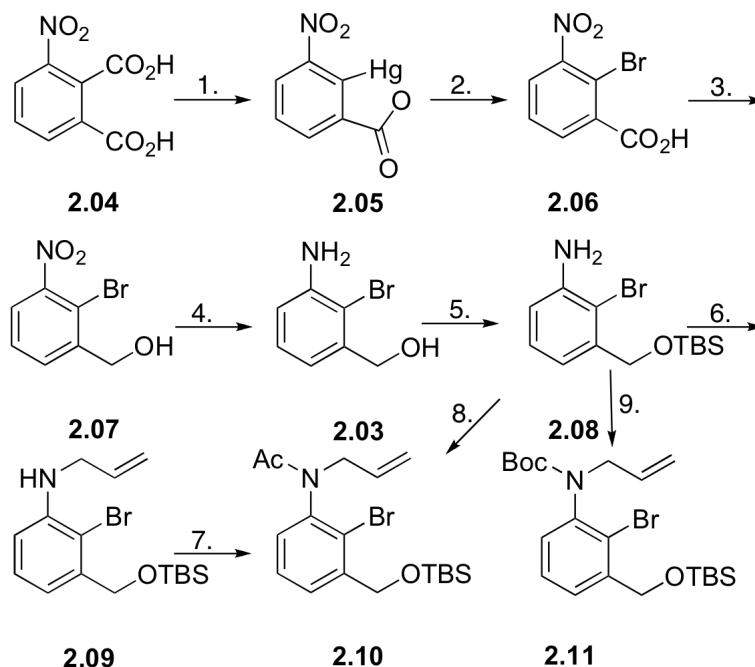
Scheme 27: Proposed Hydrogen-Bonded Transition State

Unfortunately all attempts to induce a regioselective bromination were futile under the reported conditions; TLC analysis showed multispot mixtures so the previous method of synthesizing **2.03** was employed.

2.1 Synthesis of Aromatic Cross Metathesis Partner

3-Nitrophthalic acid **2.04** was converted exclusively to 2-bromo-3-nitrobenzoic acid **2.06** in 74% yield via the organomercury compound **2.05** following the procedure of Culhane and co-workers.⁵² Reduction of carboxylic acid **2.06** with two equivalents of borane:THF complex in THF at 0°C gave the desired benzyl alcohol **2.07** in 91% yield. Reduction of the nitro moiety in **2.07** to aniline derivative **2.03** was initially tried with tin(II)chloride in ethanol,⁵³ however this proved to be unsuccessful. The use of iron powder in refluxing acetic acid and ethanol efficiently converted **2.07** to aniline **2.03** in 75% yield. Protection of the alcohol functionality of **2.03** with *tert*-butyl dimethylsilyl chloride with dimethylformamide as a solvent, due to solubility issues, occurred in a satisfactory 92% yield furnishing silyl ether **2.08**. Deprotonation with freshly formed LDA in THF followed by addition of allyl bromide gave allyl amine **2.09** in 72% yield, the *N,N*-diallyl species was isolated in 7% yield along with a mixed fraction of 10%. Subsequent amine protection with acetyl chloride gave acetamide **2.10** in 90% yield. It was found that if compound **2.09** was taken on crude and protected as its acetamide, then **2.08** could be converted directly to **2.10** in an increased yield of 80%, due to easier separation of the diallyl impurity. The *N*-Boc

analogue **2.11** was synthesised using identical methods from **2.08** in 88% yield. Thus three suitably functionalised allyl aniline derivative had been synthesised to test the proposed cross metathesis strategy.



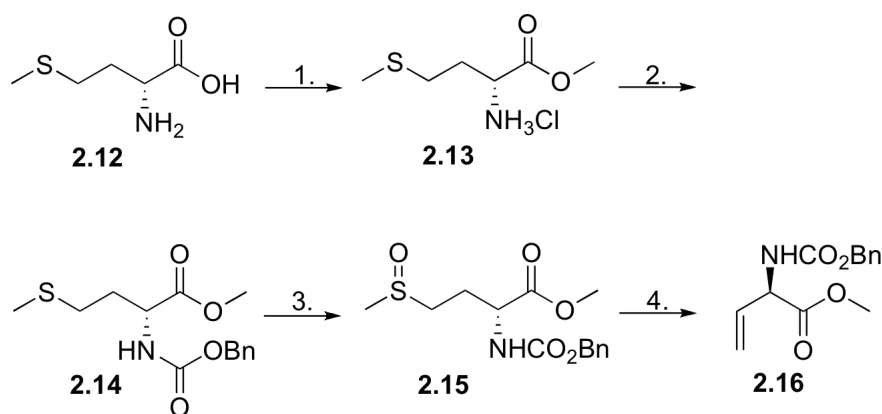
Reagents and Conditions: 1) $\text{Hg}(\text{OAc})_2$, H_2O , 170°C , 3days, 2) Br_2 , NaBr , H_2O , 100°C , 74% over 2 steps, 3) $\text{BH}_3.\text{THF}$, THF , 0°C , 2hr, 91%, 4) Fe , AcOH , EtOH , 80°C , 3hr, 75%, 5) TBSCl , DMAP , imidazole, DMF 0°C , 92%, 6) LDA , THF , -78°C to rt, allyl bromide, -78°C to rt, 2hr, 72%, 7) AcCl , THF , rt, 1hr, 80%, 8) LDA , THF , -78°C to rt, allyl bromide, -78°C to rt, AcCl , THF , rt, 1hr, 82%, 9) LDA , THF , -78°C to rt, allyl bromide, -78°C to rt, then Boc_2O , NEt_3 , MeCN , 2hr, 88%.

Scheme 28: Synthesis of Substituted Allyl Anilines.

2.2 Synthesis of Amino Acid Cross Metathesis Partner

Synthesis of the amino acid cross metathesis partner was subsequently investigated. A paper published by Rapaport *et al.* describes the synthesis of *L*-vinylglycine.⁴⁸ Initial studies following this route showed it needed refining. Starting with *D*-methionine **2.12**, the carboxylic acid group was protected as its methyl ester using a protocol published by Rachele.⁵⁴ Recrystallisation of **2.13** was problematic following Rachele's method and it was found that the most effective procedure was dropwise addition of a highly concentrated methanolic solution of **2.13** via a dropping funnel to

a stirring flask of ether. The hydrochloride salt **2.13** was dissolved in a 1:1 mixture of sodium hydrogen carbonate solution and ethyl acetate followed by dropwise addition of benzyl chloroformate yielding protected amine **2.14**. Oxidation of sulphide **2.14** to sulfoxide **2.15** was achieved using sodium metaperiodate in aqueous methanol. In the paper they report the distillation of **2.15**; however, this was not satisfactory producing a multicomponent mixture. It was found that passing the compound through a plug of silica and eluting with MeOH:CH₂Cl₂, 5:95 was the preferred method of purification. Heating pure **2.15** in a Kugelrohr distillation apparatus at 150°C at 3mmHg yielded 56% of **2.16** after column chromatography. With both partners in hand, attention turned towards the cross metathesis.



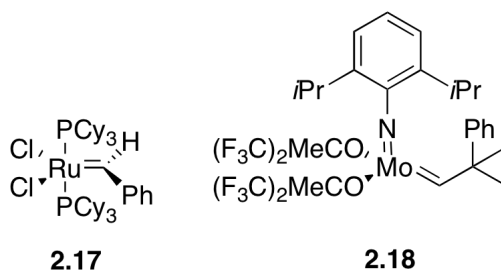
Reagents and Conditions: **1)** 2,2, demethoxy propane, HCl, MeOH, 93% **2)** benzyl chloroformate, NaHCO₃, H₂O:EtOAc, 1:1, 0°C, 88% **3)** NaIO₄, MeOH, H₂O, 92% **4)** 150°C, 3mmHg Kugelrohr distillation, 56%

Scheme 29: Synthesis of Vinylglycine

2.3 Cross Metathesis in Synthesis

Since its discovery olefin metathesis has been ubiquitous in the literature.⁵⁵ Historically it has been studied from a mechanistic standpoint⁵⁶ and from the perspective of ring opening polymerisation (ROMP).^{57, 58} Until the development of the 1st generation of commercially available catalysts such as the ruthenium benzylidene **2.17** by Grubbs *et al.*^{59, 60} and the molybdenum alkylidene **2.18** by

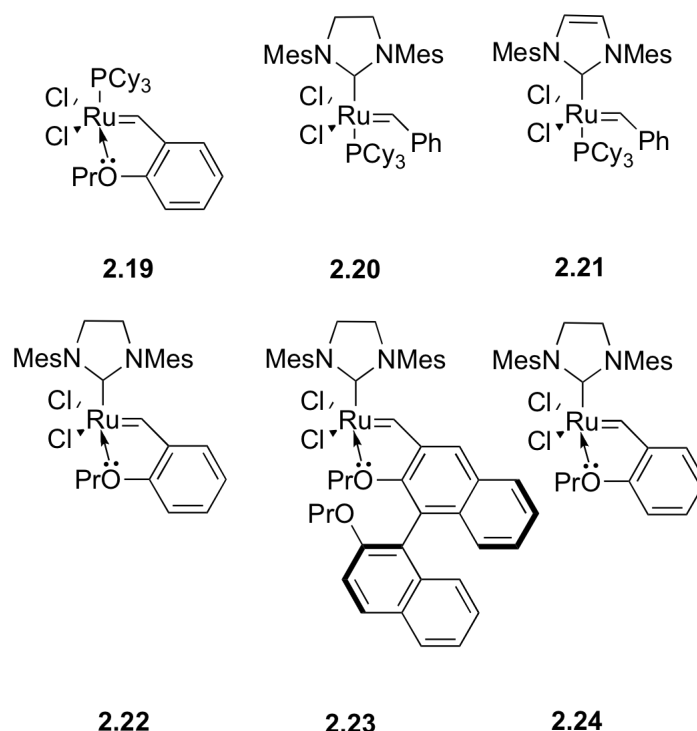
Schrock *et al.*^{61 62, 63,} which can tolerate reasonably well the diverse functionality encountered in organic synthesis, olefin metathesis in natural product synthesis was very rare. Since their introduction the realisation of alkene metathesis as an effective tool in organic synthesis began with the ring closing metathesis (RCM) of acyclic dienes for the construction of complex carbocycles and heterocycles.⁶⁴



Scheme 30

Scheme 30: First Generation Olefin-Metathesis Catalysts.

The quantity of papers concerning RCM and ROMP vastly outweighed the number reporting successful cross metatheses (CM), however the development a second generation of active and robust ruthenium catalysts **2.19** to **2.24** which combine the activity previously only associated with Schrock's molybdenum catalyst **96** with an impressive functional group tolerance has caused a surge of interest in CM as powerful synthetic tool.^{65 66,}



Scheme 31: 2nd Generation Ruthenium Alkene-Metathesis Catalysts.

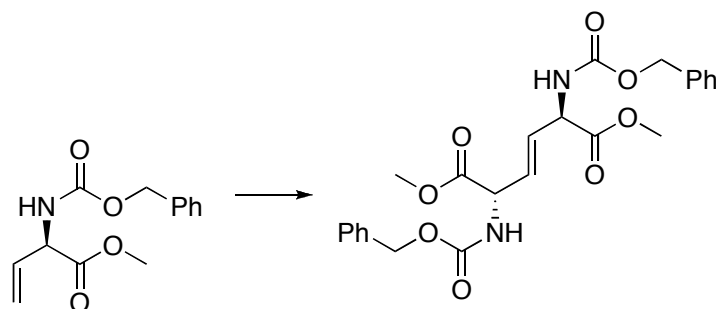
Previous work by Parsons *et al.* involving cross metathesis synthesising substituted nitro alkenes used Grubbs second-generation catalyst **2.20**⁶⁷ and previous work involving vinyl glycine derivatives also used **2.20**.^{44, 45, 46, 47} Therefore **2.20** was initially used

Grubbs and co-workers have published a useful report categorizing terminal alkenes into 4 differing classes in terms of their participation in cross metathesis: Type 1: rapid homodimerisation, homodimer participates in a subsequent metathesis reaction, Type 2: slow homodimerisation, homodimer sparingly participates in a subsequent metathesis reaction, Type 3: no homodimerisation, Type 4: olefin inert to CM and does not deactivate the catalyst (spectator).⁶⁸

2.4 Homodimerisation of Vinylglycine

On this basis vinylglycine derivative **2.16** would be described as Type 1 with respect to Grubbs second generation catalyst **2.20**, since treatment of **2.16** with 10mol% of **2.20**

gave the homodimerisation product **2.25** and it has been demonstrated that vinylglycine derivatives have been utilised in CM.^{44, 45, 46, 47}



Reagents and Conditions: **2.20** (10mol%), CH₂Cl₂, 18hr, 74%

Scheme 32: Synthesis of Homodimer **2.25**

2.5 X-Ray Crystal Structure of **2.25**

The structure of **2.25** has been confirmed by X-ray crystallography (**Figure 3**)

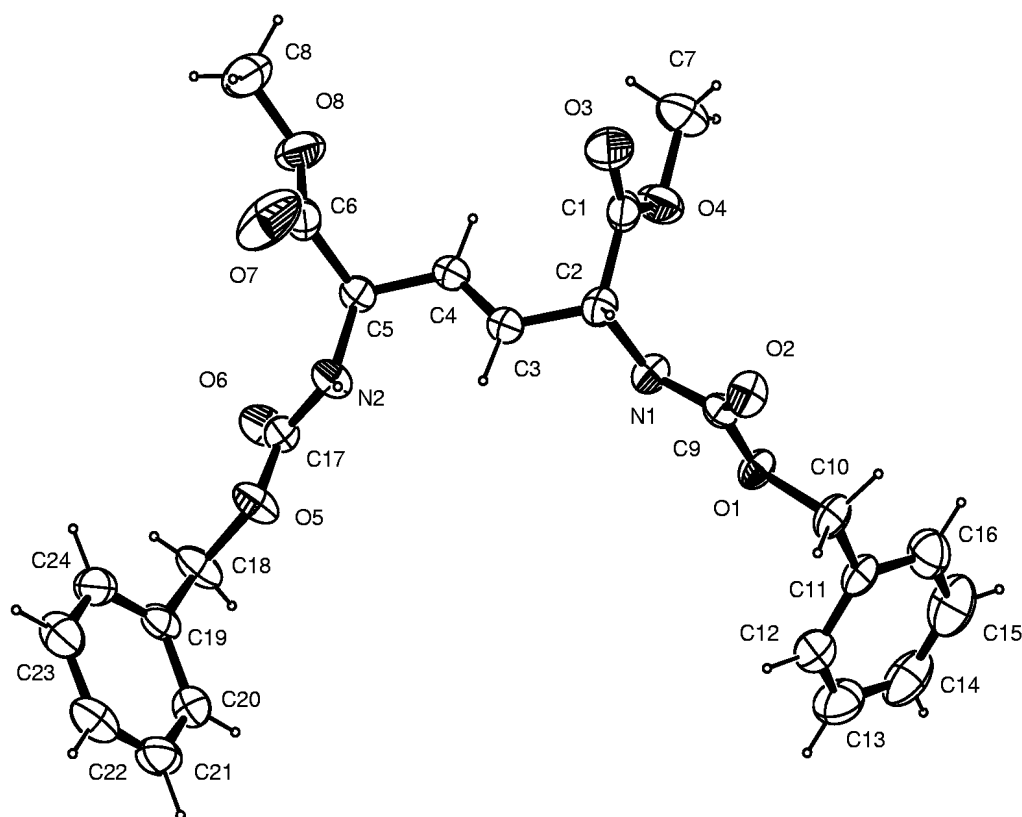
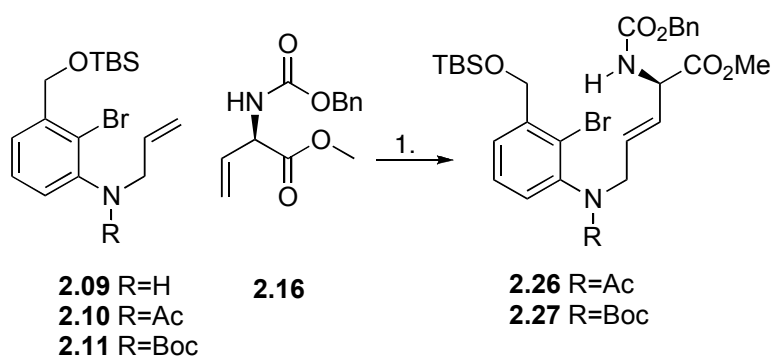


Figure 3: ORTEP Drawing of Vinyl Glycine Dimer **2.25**.

The compound **2.25** is a chiral molecule belonging to a monoclinic crystal system with a C₂ (No.5) space group. The dimer has potential use as a chiral auxiliary.

2.6 Cross Metathesis of Vinyl Glycine and Allyl Amide Analogues

Initially allyl amine substrate **2.09** was tested; unfortunately this gave an inseparable mixture due to similar polarity of starting materials and product. Acetamide **2.10** gave 62% of **2.26** after treatment with 10mol% Grubbs II **2.20**, whilst carbamate **2.11** gave 56% of **2.27**. A publication by Fukuyama *et al.* on a total synthesis of kainic acid utilises a RCM metathesis of an allylcarbamate,⁶⁹ it was found that Grubbs-Hoyveda II catalyst **2.22** at an elevated temperature in DCE needed very low catalyst loadings. This was tested on our system, with **2.10** and **2.11**, and gave a multispot component mixture, possibly attributed to the higher temperature leading to an isomerisation of the double bond into conjugation. The outcomes are summarised in table 1.



Reagents and Conditions: 1) See Table 1

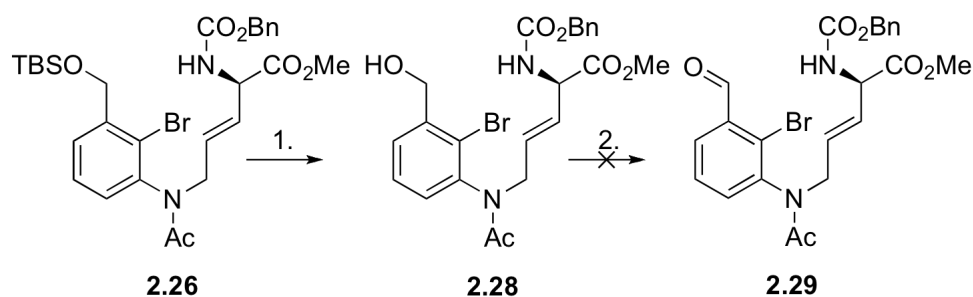
Scheme 33: Cross-Metathesis of Vinyl Glycine

R	Catalyst	Loading/%	Solvent	Temp/°C	Time/hr	Yield/%
H	2.20	10	DCM	40	18	Inseparable
Ac	2.20	10	DCM	40	18	62
Ac	2.22	5	DCE	80	18	Decomposition
Boc	2.20	10	DCM	40	18	54
Boc	2.22	5	DCE	80	18	Decomposition

Table 1: Results of Cross Metathesis of Allyl Amide Analogues.

2.7 Elaboration of 2.26

With the allyl amino acid side chain installed our attention turned towards elaboration of the silyl ether. Deprotection of **2.26** with hydrofluoric acid in acetonitrile gave 90% of benzyl alcohol **2.28**. Attempts at oxidation of the benzylic position with manganese(IV)oxide in both THF and methylene dichloride gave multispot component mixtures possibly due the formation of a nitrogen based radical cation. Ba(KMnO₄) gave a similar result.

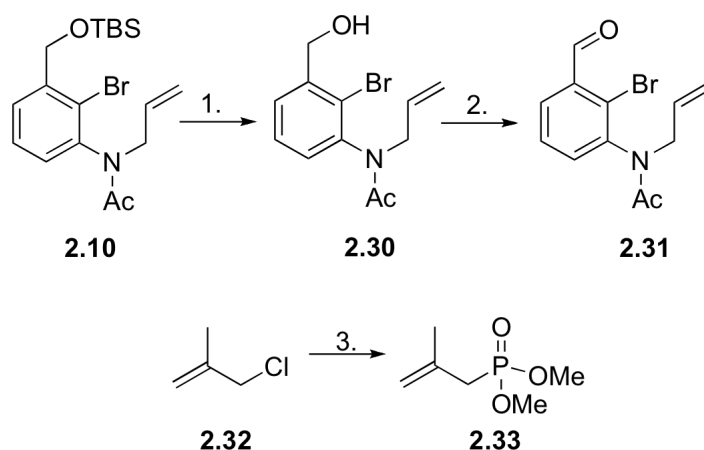


Reagents and Conditions: 1) HF, MeCN, rt, 18hr, 90% 2) MnO₂, THF, rt, 18hr

Scheme 34: Elaboration of Cross-Metathesis Product

2.8 Retrosynthesis part II

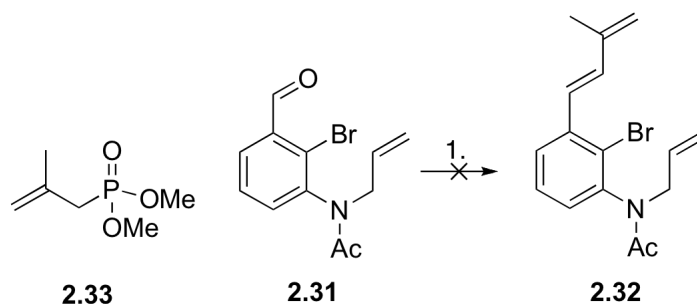
Concurrent experiments indicated that a different retrosynthetic plan should be implemented. Deprotection of **2.10** with hydrofluoric acid in acetonitrile, followed by oxidation with manganese(IV)oxide in tetrahydrofuran yielded benzaldehyde **2.31** in 78% yield from silyl ether **2.10**. Phosphonate **2.33** for the Horner-Wadsworth-Emmons reaction was prepared using a method published by Yokomatsu *et al.* utilising an iodide catalysed Arbuzov reaction.⁷⁰



Reagents and Conditions **1)** HF, MecN, rt, 2hr, 97% **2)** MnO₂, THF, rt, 18hr, 82%
3) KI, P(OMe)₃, (CH₃)₂CO:MeCN, 10:8, rt for 12h then 60°C for 6h, 87%

Scheme 35: Preparation of Horner-Wadsworth-Emmons reaction precursors.

Following a procedure published by West and Wang in their synthesis of (*E*)-1,3-dienes,⁷¹ deprotonation of phosphonate **2.33** with butyllithium in THF at -78°C followed by addition *via* canular of aldehyde **2.31** in HMPA at -78°C gave, by TLC analysis, complete consumption of starting material **2.31** and the appearance of a single less polar product. Isolation by column chromatography yielded only 20% by mass of the isolated product, which rapidly decomposed on standing in the freezer meaning characterisation was impossible. This observation and the apparent difficulty in oxidising **2.28**, led us to back to the blackboard.

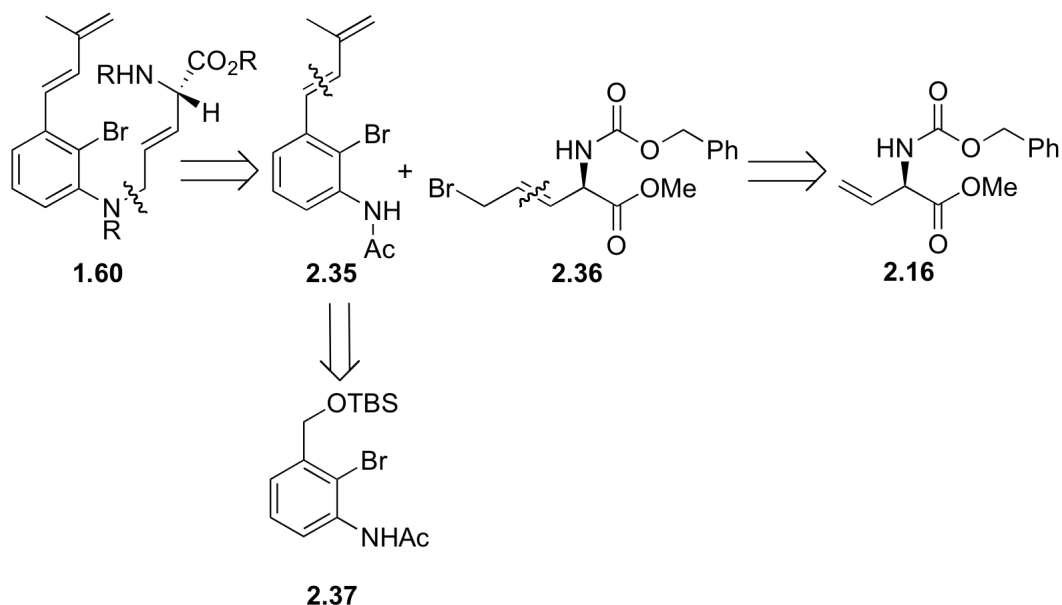


Reagents and Conditions: **1)** **2.33**, nBuLi, -78°C, 15min, then **2.31** in HMPA, -78°C to rt, decomp.

Scheme 36: Attempted Synthesis of Triene Model

It was conceived that a synthon of the proposed vinyl aziridine **1.65** could be prepared by a cross metathesis of allyl bromide, type 1 under Grubbs classification,⁶⁸ with

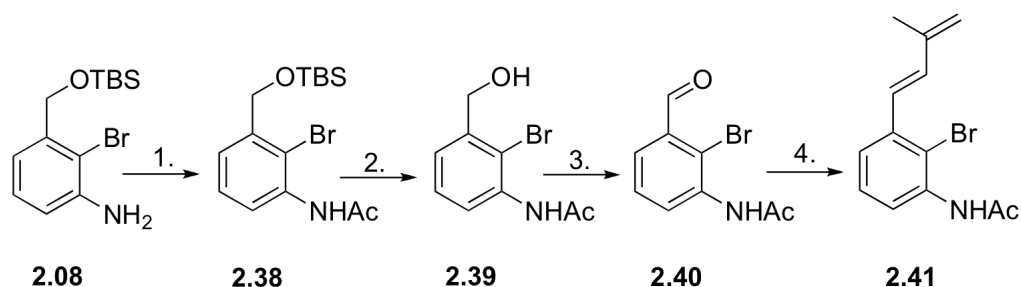
vinyl glycine **2.16**. The Horner-Wadworth-Emmons reaction would be utilised prior to instalment of allyl amine side chain.



Scheme 37: 2nd Generation Retrosynthesis of α -CPA **1**.

2.9 Synthesis of Diene **2.41**

The construction of intermediate **2.41** was a relatively trivial process. Protection of aniline **2.08** as its acetamide followed by deprotection of the silyl ether **2.38**, and subsequent oxidation of benzyl alcohol **2.39** furnished benzaldehyde derivative **2.40** in 76% yield from **2.08**. Following the protocol of West and Wang,⁷⁰ aldehyde **2.40** was converted to 1,3 diene **2.41** in 79% yield.

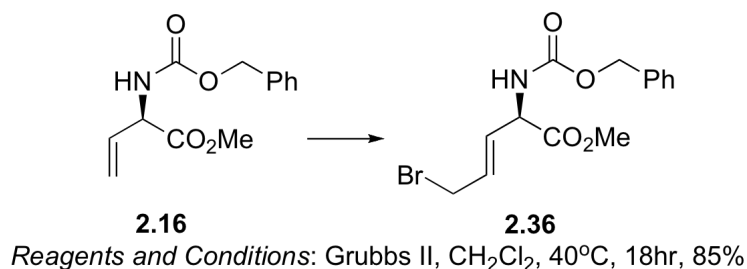


Reagents and Conditions: 1) AcCl, THF, rt, 2hr, 91%, 2) HF, MeCN, rt, 2hr, 95% 3) MnO₂, THF, rt, 18hr 88% 4) **2.33**, nBuLi, -78°C, 15min, then **2.40** in HMPA, -78°C to rt, 79%

Scheme 38: Synthesis of Diene **2.41**

2.10 Synthesis of 2.36

The valuable intermediate **2.36** was synthesised from vinylglycine **2.16** in 85% yield using 10 equivalents of allyl bromide in the presence of 10mol% of Grubbs second generation catalyst **2.20**.



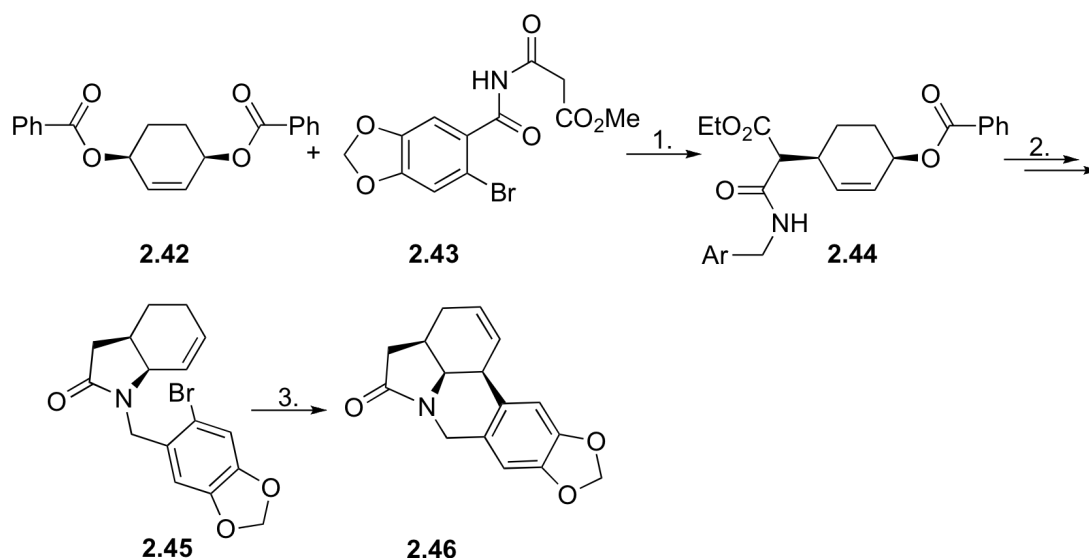
Scheme 39: Cross Metathesis of Allyl Bromide with Vinyl Glycine.

2.11 Nucleophilic Substitution Route

Originally a similar strategy for the installation of the allyl group onto **2.08** was implemented. Treatment of **2.41** with one equivalent of LDA at -78°C, followed by dropwise addition of **2.36** in THF via canula at -78°C, resulted in the isolation of just the two starting materials. It is known that Finkelstein conditions can assist nucleophilic displacement of bromides.⁷² Premixing of bromide **2.36** with one equivalent potassium iodide for one hour in THF, followed by dropwise addition to the lithiate of **2.41** at -78°C in THF was also a futile process, with no conversion to the desired product **1.60**. It was perceived that possibly a π -allyl palladium approach could solve our dilemma.

2.12 Palladium in Synthesis

The majority of fundamental processes catalysed by palladium were well established by the mid-1980's; however their use and acceptance as synthetic procedures was minimal until the mid-1990's, whereas today palladium is one the most useful metals in a chemist's armoury. A beautiful combination of palladium catalysed processes is demonstrated towards the synthesis of (+)- δ -lycorane.⁷³

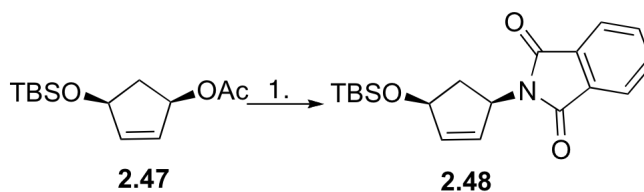


Reagents and Conditions: **1)** Pd(OAc)₂, (S)-BINAPO, LDA (2.6eq), **2.42** (1eq), **2.43** (2.6eq), THF, 0°C, 1hr, 66% (crude) **2)** Pd(OAc)₂, dppb, NaH, DMF, 50°C, 5h, 81% **3)** Pd(OAc)₂, PPh₃, *i*Pr₂NEt, DMF, 100°C, 7.5hr, 72%

Scheme 40: Palladium in the Synthesis of (+)-δ-Lycorane.

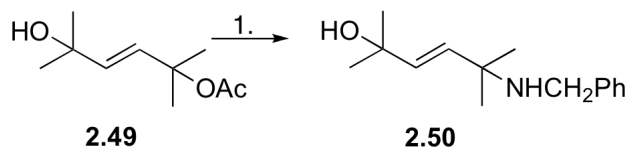
2.13 π -Allyl Palladium Catalysed Aminations

On inspection of the literature for guidance in palladium catalysed allylic aminations, several sets of conditions all with allyl acetates were found:



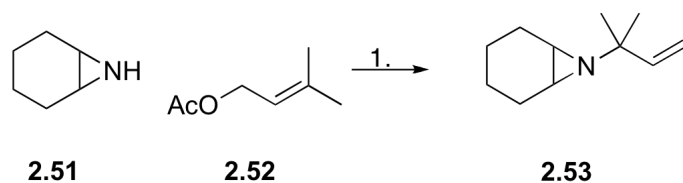
Reagents and Conditions: **1)** Pd₂dba₂ (5mol%), dppb (10mol%), phthalimide(2.1eq.), THF, 75°C, 85%

Scheme 41: Pd₂dba₂ with dppb.⁷⁴



Reagents and Conditions: **1)** Pd(DIPHOS)₂ (5mol%), PhCH₂NH₂ (1.1eq), THF, 65°C, 76%

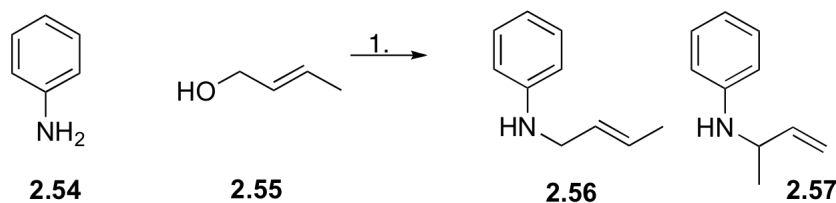
Scheme 42: Pd(DIPHOS)₂ in THF.⁷⁵



Reagents and Conditions: 1) [Pd(η³-C₃H₅)Cl]₂ (1mol%) BINAP (2mol%), THF, rt, 89%

Scheme 43: [Pd(η³-C₃H₅)Cl]₂ with BINAP.⁷⁶

An interesting alternative using allyl alcohols utilising Ti(O^{*i*}Pr)₄ has been reported by Hung and Yang.⁷⁷

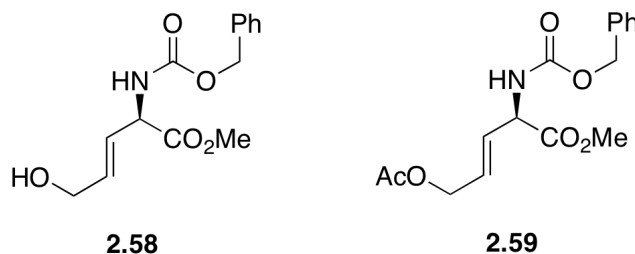


*Reagents and Conditions: 1) Pd(OAc)₂ (1mol%), PPh₃ (4mol%), Ti(O^{*i*}Pr)₄ (25mol%) MS4A°, PhH, 97% (2.55:2.56 83:17)*

Scheme 44: Pd(OAc)₂ and Ti(O^{*i*}Pr)₄.

2.14 Synthesis of 2.58

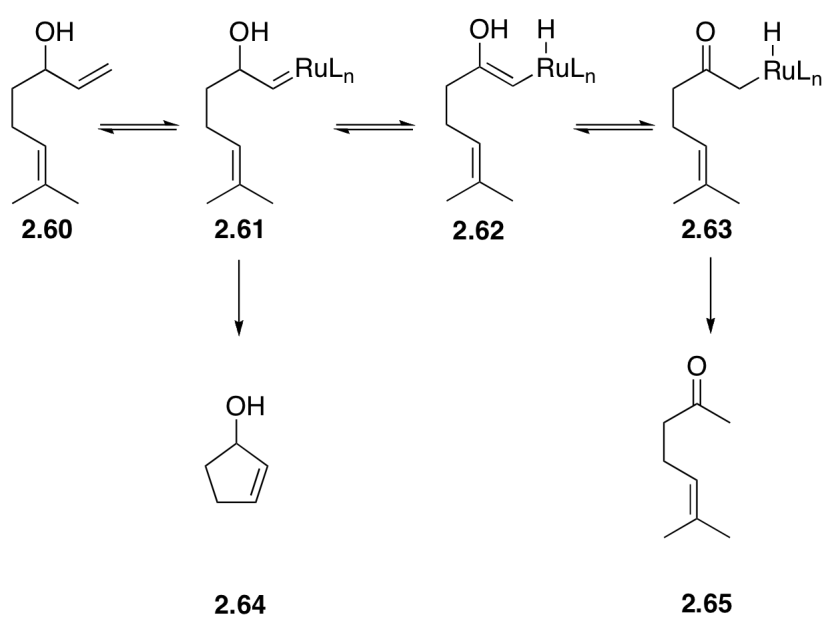
On this basis the synthesis of both **2.58** and **2.59** was required.



Scheme 45: Required Synthons for π-Allyl Palladium Approach.

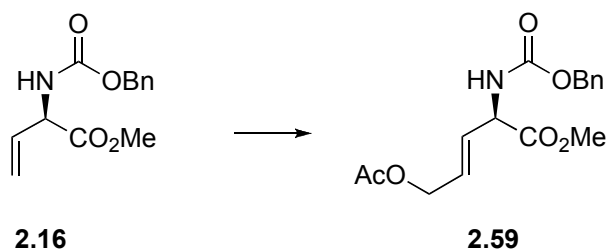
Using the same procedure as for the production of **2.36**, treatment of ten equivalents of allyl alcohol with one equivalent of vinyl glycine **2.16** with **2.20** 10mol% yielded none of the desired CM product **2.58**. This could be attributed to a reported non-metathetic process of the degradation of terminal allyl alcohols to methyl ketones first reported by Hoye and Zhao.⁷⁸

Hoye and Zhao discovered, whilst conducting systematic studies on allylic substituent effects on the RCM of substrates of type **2.60**, that two products were formed **2.64** and **2.65** in ratio of 2:3. An interesting side-reaction occurred that induced the overall transformation of **2.60** to **2.65**, postulated to occur through the mechanism outlined in **Scheme 46**.



Scheme 46: Proposed Mechanism of Grubbs Catalysed Isomerisation.

Under identical conditions, treatment of ten equivalents of allyl acetate and one equivalent of vinyl glycine **2.16** with **2.20** 10mol%, yielded 36% of the desired CM product **2.59**. This low yield could be attributed the classification of allyl acetate as Type 2 with respect to **2.20** since approximately 60% of the allyl acetate homodimer was isolated.

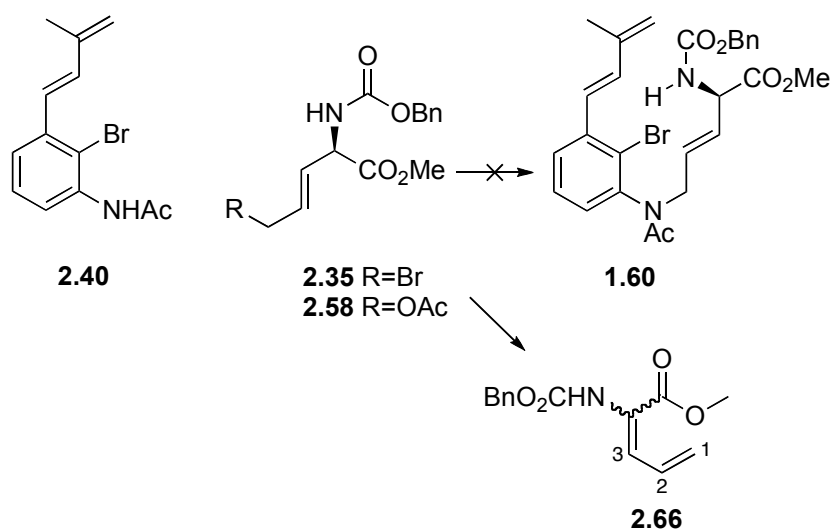


Reagents and Conditions: **2.20** (10mol%), Allyl Acetate, CH₂Cl₂, 40°C, 18hr, 36%

Scheme 47: Synthesis of **2.59**

2.15 π -Allyl Palladium Route to **1.60**

Attempts to couple **2.36** or **2.59** with **2.41** under a variety of the reported conditions for palladium catalysed allylic aminations unfortunately only resulted in diene **2.66** in around 75% yield and none of the desired radical precursor **1.60**.



Reagents and Conditions: See Table 2

Scheme 48: Palladium Catalysed Coupling Towards **1.60**

Entry	Compound	Reagents and Conditions	Product	Yield/ %
1	2.36	Pd ₂ (dba) ₃ , dppb,	2.66	78
2	2.36	NaH, Pd(OAc) ₂ , PPh ₃ , K ₂ CO ₃ , MeCN	2.66	72
3	2.36	NaH, Pd(OAc) ₂ , PPh ₃ , K ₂ CO ₃ , THF	2.66	75
4	2.36	Pd ₂ (dba) ₃ , SPhos, NaH	2.66	81
5	2.59	Pd ₂ (dba) ₃ , dppb,	2.66	76
6	2.59	NaH, Pd(OAc) ₂ , PPh ₃ , K ₂ CO ₃ , MeCN	2.66	75
7	2.59	NaH, Pd(OAc) ₂ , PPh ₃ , K ₂ CO ₃ , THF	2.66	71
8	2.59	Pd ₂ (dba) ₃ , SPhos, NaH	2.66	79

Table 2: Results of Palladium Catalysed Allylic Amination.

2.16 Discussion of ¹H-NMR of 2.66

The ¹H-NMR spectrum of **2.66** (The atoms are numbered in **Scheme 48**) is delineated in **Figure 4**. The indicative regions are: the a doublet (J=11.2Hz) at 7.00 ppm that is assigned to H-3, a doublet of triplets (J=17.0 and 10.7Hz) at 6.59ppm which is attributed to H-2, a singlet at 6.41ppm from the NH, a doublet (J=16.9Hz) at 5.60ppm assigned to H-1_E and a doublet (J=10.0Hz) at 5.48 ppm from H-1_Z.

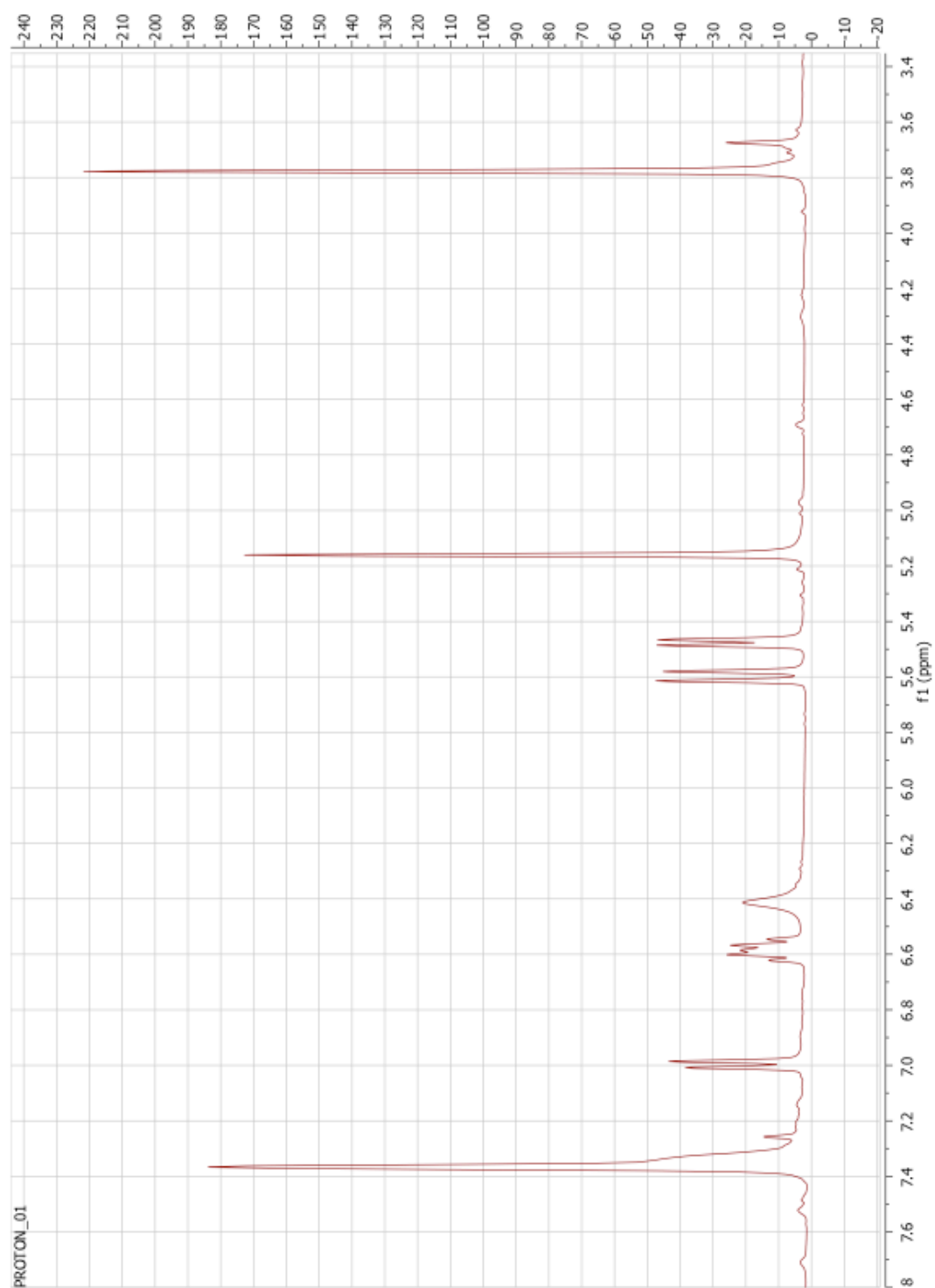
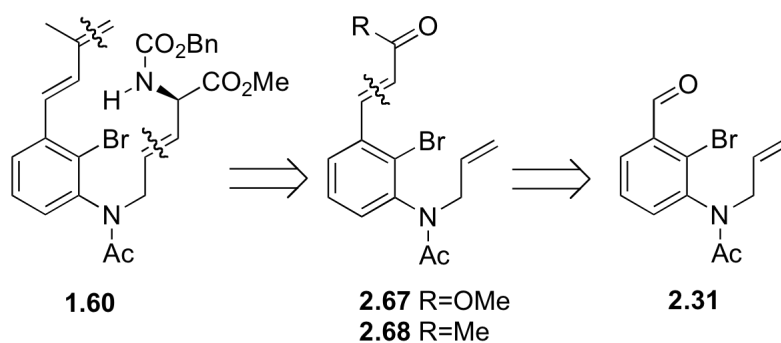


Figure 4: ^1H -NMR Spectrum of 2.66

2.17 Retrosynthesis Part III

On further retrosynthetic inspection of **1.60**, it was considered that if the terminal olefin was masked, to avoid undesired side reactions, then the double bond of the aniline side chain could be disconnected using the alkene metathesis strategy leading to intermediates **2.67** and **2.68**. The reintroduction of the required functionality is possible through either the methyl ester **2.67**, where addition of MeLi will install the desired dimethyl geminal unit as tertiary alcohol or *via* the methyl ketone **2.68** where either addition of MeLi or a Wittig reaction will establish the desired functionality. This approach would hopefully prevent the oxidation problems previously encountered with **2.26** would be avoided since the familiar CM strategy would be implemented afterwards. Both compounds **2.67** and **2.68** are available *via* a Wittig reaction from previously synthesised aldehyde **2.31**.

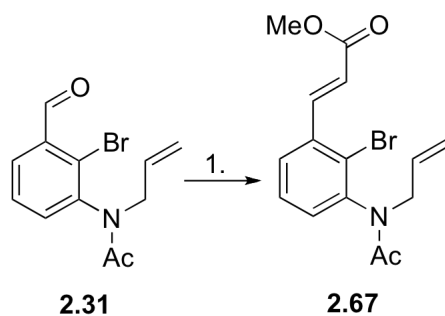


Scheme 48

Scheme 49: 3rd Generation Retrosynthesis of α -CPA **1**.

2.18 Synthesis of Methyl Ester **2.67**

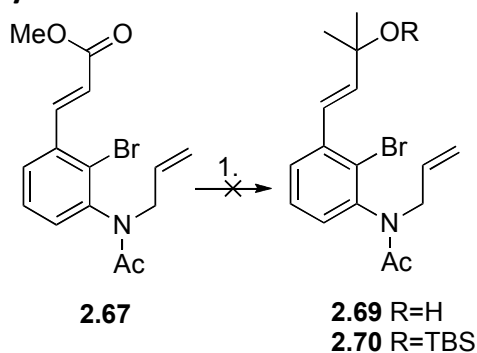
Treatment of aldehyde **2.31** with the required phosphorane produced methyl ester **2.67** in 89% yield. Several sets of conditions were tried for the conversion of **2.67** to the tertiary alcohol **2.69**.



Reagents and Conditions: 1) methyl (triphenylphosphoranylidene)acetate, CH₂Cl₂, rt, 18hr, 89%.

Scheme 50: Synthesis of Methyl Ester **2.67**.

2.19 Addition of Methyllithium to **2.67**



Reagents and Conditions: 1) See Table 3

Scheme 51: Attempted Synthesis of Tertiary Alcohol

Initially compound **2.67** was dissolved in THF and cooled to -78°C; 2.2 equivalents of methyllithium was added dropwise and the newly formed bright yellow solution was allowed to warm to 0°C upon which it turned to a murky brown mixture, possibly due to THF decomposition; α -deprotonation followed by a retro 2+3 cycloaddition yielding ethylene and the enolate of acetaldehyde.⁷⁹ TLC analysis revealed a multi component mixture the separation of which was worthless. Following a protocol published by T. A. Chevchouk *et al.*⁸⁰ methyllithium was added to diethyl ether and cooled to 0°C, addition of a solution of **2.67** in diethyl ether immediately resulted in the brown murky mixture observed previously. The first method was modified by quenching at -78°C with a pre-cooled saturated ammonium chloride solution, TLC analysis revealed a significantly cleaner reaction. Isolation by standard methods

produced a bright yellow oil which decomposed rapidly. It thought that possibly the tertiary allylic alcohol was possibly eliminating to the unstable triene **2.31**. A potential inhibition of this suspected elimination would be the protection of the potentially formed alcohol functionality **2.69** as the silyl ether **2.70**.

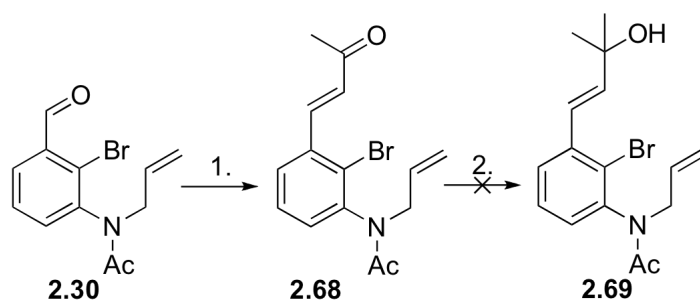
A report by Corey and co-workers suggests that the best reagent for the protection of tertiary alcohols is *tert*-butyldimethylsilyl triflate.⁸¹ On this basis using the original approach, once TLC analysis revealed complete consumption of starting material approximately 30 minutes after the final addition of methyllithium, four equivalents of 2,6-lutidine followed by three equivalents of TBSOTf were added; unfortunately this resulted in the familiar multicomponent mixture after work up.

Entry	Reagents and Conditions	Yield
1	MeLi (2.2 eq), THF, -78°C to 0°C	Decomp.
2	MeLi (2.2 eq), Et ₂ O, 0°C	Decomp.
3	MeLi (2.2 eq), THF, -78°C then sat.NH ₄ Cl _(aq.) , -78°C	Decomp.
4	MeLi (2.2 eq), THF, -78°C, 2,6-lutidine (4.0 eq), TBSOTf (3.0 eq)	Decomp.

Table 3: Results of Attempted Dimethylation of 2.67.

2.20 Synthesis of Methyl Ketone 2.68

Due to the difficulty encountered in transforming α,β -unsaturated methyl ester **2.67** into either tertiary alcohol **2.69** or silyl ether **2.70**, methyl ketone **2.68** was explored. Under standard conditions aldehyde **2.30** was converted in to methyl ketone **2.68** in 92% yield.

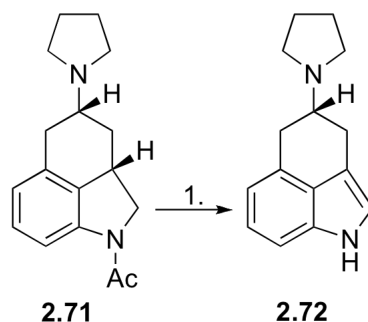


Reagents and Conditions: 1) 1-(triphenylphosphoranylidene)acetone, CH₂Cl₂, rt, 18hr, 92%,
2) MeLi, THF, -78°C.

Scheme 52: Synthesis of Methyl Ketone **2.68**.

2.21 Indolic Oxidation

At this stage in the project there was a concern about the installation of the indolic double bond after radical cyclisation. It has been demonstrated by Parsons *et al.* that tetracycle **2.71** can be oxidised to **2.72** but in a low yield.^{25, 26} It has also been found that **2.71** was aerielly oxidised to **2.72** during amide hydrolysis after two weeks.



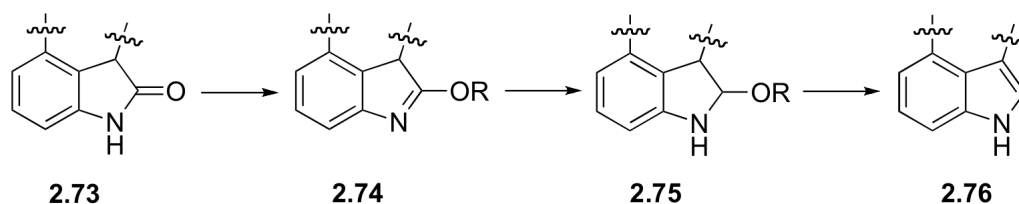
Reagents and Conditions: 1) NaOH_(aq.), MeOH, then MnO₂, CH₂Cl₂, rt, 35%

Scheme 53: Indolic Oxidation

2.22 Indolinone Strategy

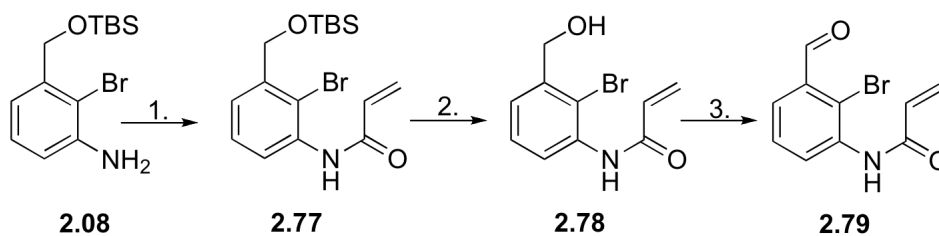
Due to low yield observed during the transformation of **2.71** to indole **2.72** it was thought that if an indolinone **2.73** was prepared, protection of the amide as an iminoether **2.74**, followed by reduction of the iminoether with sodium cyanoborohydride would yield the unstable aminoalcohol **2.75** which would spontaneously aromatise to indole **2.76**. This premise has a secondary advantage, if

the iminol ether was installed prior to the radical cyclisation, since the precursor would be held in a rigid conjugated system topographically assisting the reaction.



Scheme 54: Proposed Indolinone to Indole Strategy.

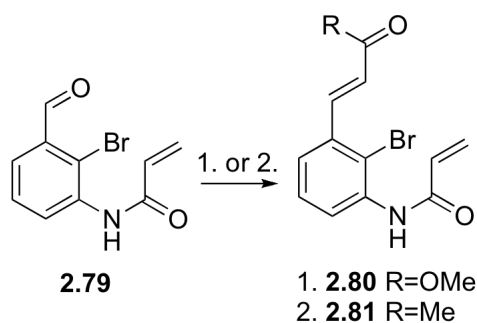
To test this hypothesis, firstly acrylamide **2.77** was synthesised by traditional methods. Acryloyl chloride was freshly prepared by treatment of acrylic acid with oxalyl chloride in dichloromethane followed by removal of unreacted oxalyl chloride under reduced pressure.⁸² The acid chloride was then dissolved in CH_2Cl_2 , triethylamine was added followed by aniline **2.08**, yielding acrylamide **2.77** in 80 % yield. Deprotection with HF and subsequent oxidation with MnO_2 yielded **2.49** in 79% yield from silyl ether **2.77**.



Reagents and Conditions: 1) acryloyl chloride, CH_2Cl_2 , NEt_3 , rt, 2hr, 80%, 2) HF, MeCN, rt, 2hr, 94%, 3) MnO_2 , THF, 84%

Scheme 55: Synthesis of Benzaldehyde **2.79**

Benzaldehyde **2.79** was elaborated to both the methyl ester **2.80** and methyl ketone **2.81**.



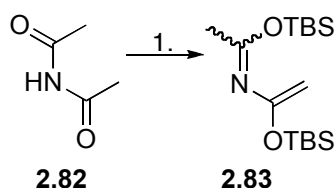
Reagents and Conditions: **1**) methyl (triphenylphosphoranylidene)acetate, CH₂Cl₂, rt, 3hr, 86%, **2**) 1-(triphenylphosphoranylidene)acetone, CH₂Cl₂, rt, 3hr, 82%,

Scheme 56: Synthesis of **2.80** and **2.81**

With silyl ether **2.77**, methyl ester **2.80** and methyl ketone **2.81** in hand, the formation of an iminol ether such as **2.74** was investigated.

2.23 Synthesis of Iminol Ethers

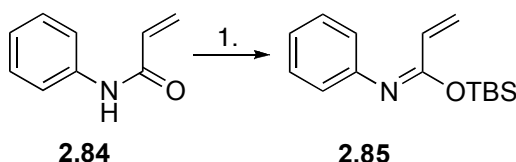
The synthesis of silyl iminol ether **2.83** was first reported by Ghosez and co-workers,⁸³ utilised as a diene in hetero-Diels-Alder reactions.



Reagents and Conditions: **1**) TBSOTf, NEt₃, Et₂O, 86%

Scheme 57: TBSOTf and NEt₃ in Et₂O.

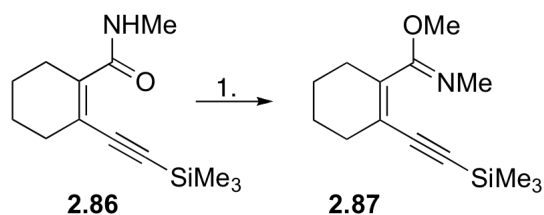
Takasu *et al.* using sodium hydride and tert-butyldimethyl silyl chloride in THF have reported the construction of 1-aza-2-siloxybutadienes.⁸⁴



Reagents and Conditions: **1**) NaH (1.0 eq), THF, rt then TBSCl (1.0 eq), rt, 69%

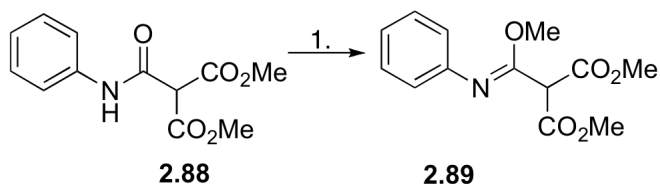
Scheme 58: TBSCl and NaH in THF.

Several methylating agents have also been described in the preparation of methyl imino ethers:



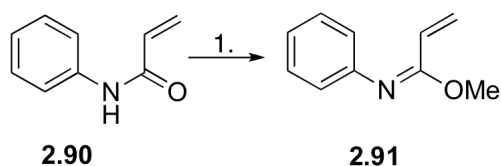
Reagents and Conditions: 1) MeOTf, CH₂Cl₂, rt, 144hr, 85%

Scheme 59: MeOTf in CH₂Cl₂.⁸⁵



Reagents and Conditions: 1) CH₂N₂, Et₂O, 0°C, 12hr, then rt, 12hr, 78%

Scheme 60: Diazomethane in Diethyl Ether⁸⁶



Reagents and Conditions: 1) Me₃OBF₄, CH₂Cl₂, rt, 20hr, 79%

Scheme 61: Meerweins' salt in CH₂Cl₂⁸⁷

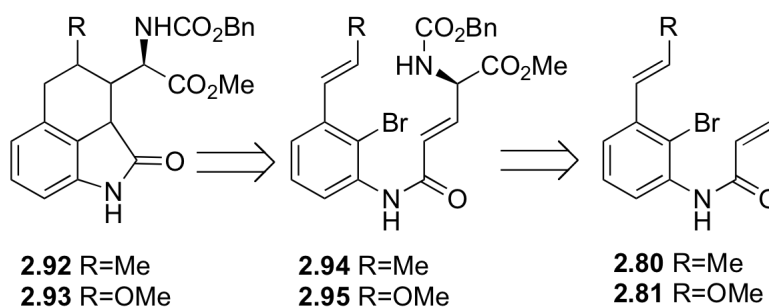
These results encouraged our confidence in installing an iminol ether moiety. Initially compound **2.77** was investigated; unfortunately no iminol silyl ether was isolated under any of the published procedures. Treatment of **2.77** with Meerwein salt in ether⁵⁵ resulted in deprotection of the silyl ether forming benzyl alcohol **2.78**. Treatment of methyl ester **2.80** under silylating conditions only resulted in recovery of starting material. Both methyl ketone **2.80** and methyl ester **2.81** only produced starting material when treated with Meerweins' salt. **Table 4**

Entry	Compound	Reagents and Conditions	Product	Yield/ %
1	2.77	2,6-lutidine, TBSOTf, DCM	SM	N/A
2	2.77	TBSOTf, NEt ₃ , Et ₂ O	SM	N/A
3	2.77	TBSCl, NaH, THF	SM	N/A
4	2.77	Meerweins' salt, DCM	2.78	24
5	2.80	2,6-lutidine, TBSOTf, DCM	SM	N/A
6	2.80	TBSCl, NaH, THF	SM	N/A
7	2.80	TBSOTf, NaH, THF	SM	N/A
8	2.80	Meerwein' salt, DCM	SM	N/A

Table 4: Results of Attempted Formation of an Iminol Ether.

2.24 Retrosynthesis Part IV

An alternative approach would be to perform the cross metathesis first between either methyl ester **2.80** or methyl ketone **2.81** and vinyl glycine derivative **2.16** and once indolinone **2.92** or **2.93** had been synthesised there would be more options to transform it into the required indole. Following the same retrosynthetic analysis **2.92** or **2.93** would be prepared by a radical cyclisation from its respective precursor, available from previously synthesised **2.80** or **2.81**.



Scheme 62: 4th Generation Retrosynthesis of α -CPA **1**.

With this strategy in mind, tertiary alcohol **2.96** was required since it already contains the necessary geminal dimethyl unit prior to radical cyclisation. Tertiary alcohol **2.96**

was prepared in 82% yield by addition of two equivalents of methyllithium to a solution of methyl ketone **2.81** at -78°C.

2.25 X-Ray Crystal Structure of Tertiary Alcohol

Compound **2.96** crystallised from a diethyl ether/hexane mixture and the structure was confirmed by X-ray analysis, it has triclinic crystal system and belongs to the $P\bar{1}$ (No.2) space group. There are two independent molecules with essentially the same geometry with hydroxyl hydrogen atoms disordered over two sites.

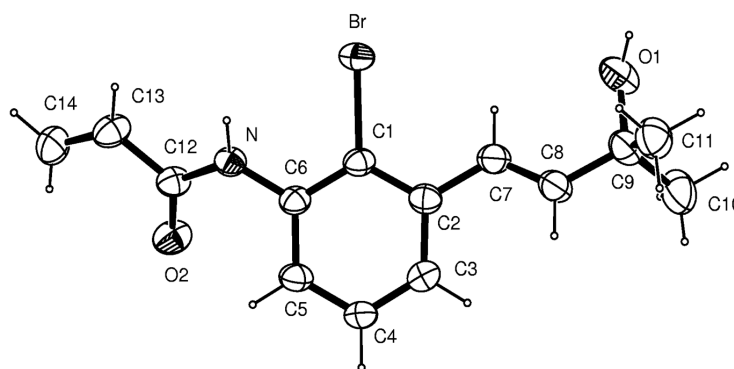
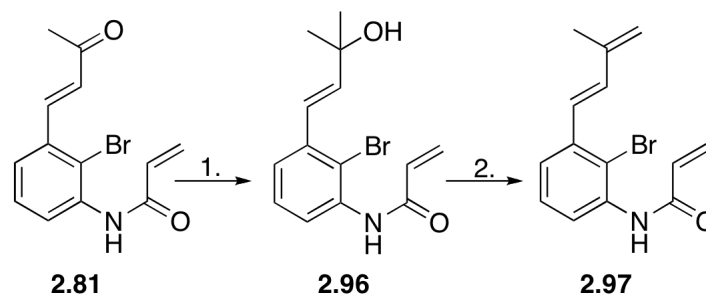


Figure 5: ORTEP Drawing of Tertiary Alcohol **2.96**.

2.26 Formation of Triene **2.97**

Protection of allylic alcohol **2.96**, resulted in the formation of triene **2.97** in 22% yield. It is assumed that this came from the production of triflic acid, protonating alcohol **2.96** resulting in elimination of water to create a tertiary allylic cation which loses a proton forming triene **2.97**.

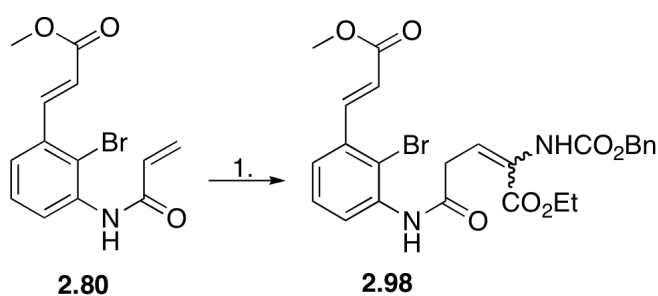


Reagents and Conditions: 1) MeLi, THF, -78°C, 2hr, 82%,
2) TBSOTf, 2,6-Lutidine, rt, 18hr, 22%

Scheme 63: Synthesis of Triene **2.97**

2.27 Cross Metathesis of Acetamide 2.81

The proposed cross metathesis was initially tested on methyl ester **2.80**; treatment of **2.80** and **2.16** with 10mol% of Grubbs second generation catalyst **2.20** in dichloromethane for eighteen hours showed by TLC analysis the formation of one major polar product and remaining starting material. Isolation by column chromatography followed by trituration with pentane yielded a white solid. ^1H -NMR spectroscopy showed three indicative peaks but unfortunately not of the desired product. During the course of the reaction after the cross metathesis had occurred, isomerisation of the double bond took place leading to enamine **2.98** in 63% yield.



Reagents and Conditions: 1) Grubbs II, CH_2Cl_2 , 40°C , 18hr, 63%

Scheme 64: Isomerised CM Product

2.28 Discussion of the ^1H -NMR of **2.98**

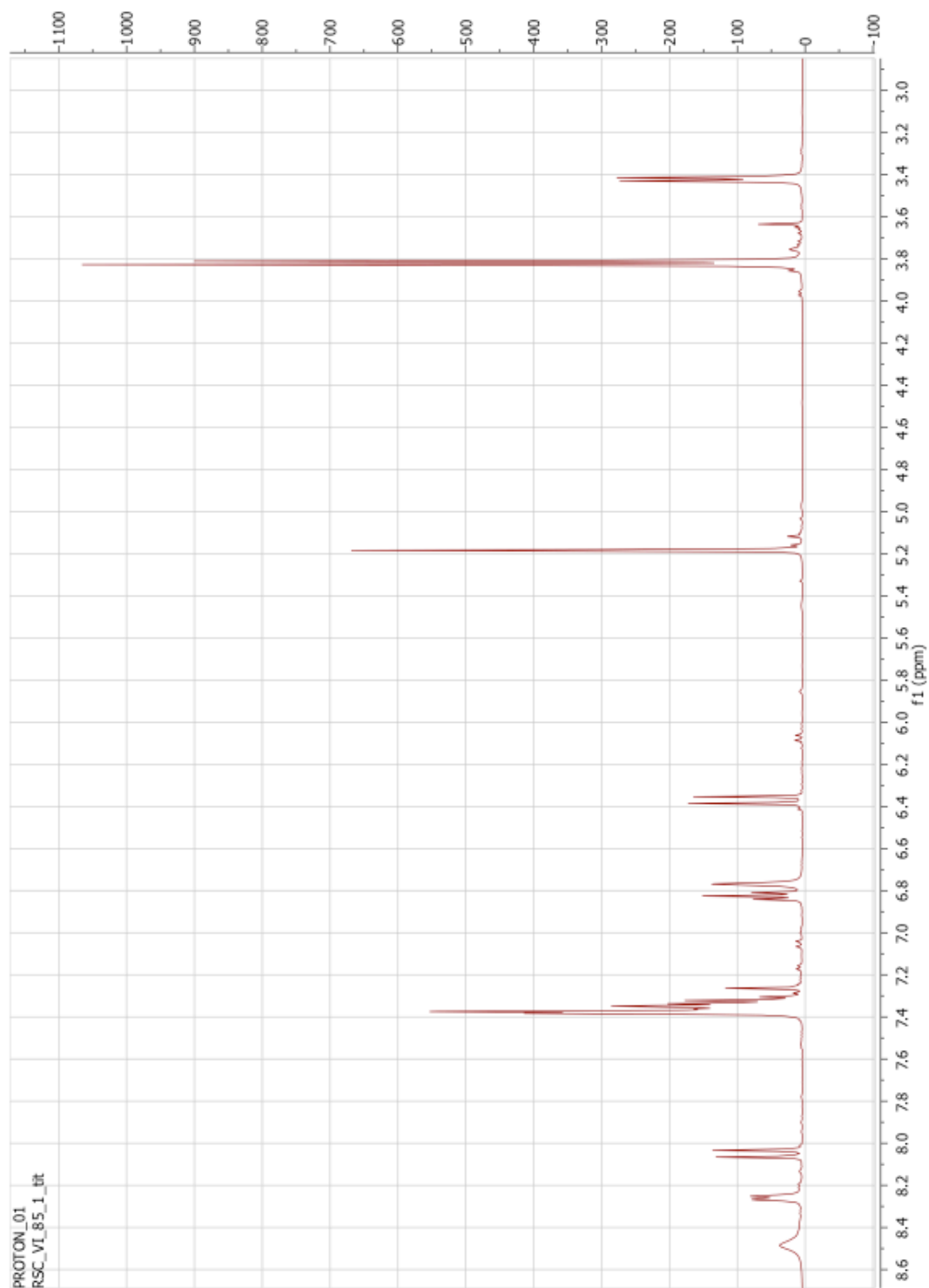


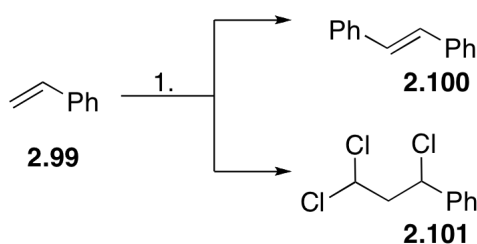
Figure 6: ^1H -NMR of enamine **2.98**

The ^1H -NMR of enamine **2.98** is delineated above, instead of the expected AX system for the trans alkene normally formed from a CM; an A_2X system was

observed, between the doublet ($J=7.6\text{Hz}$) at 3.42ppm and the triplet at 6.83ppm ($J=7.7\text{Hz}$), which is indicative of the CH_2CH proposed. An additional refining factor is the shift of the NH signal from 5.40ppm to 6.71ppm due to the conjugation, of the nitrogen lone pair with the double bond, introduced by the isomerisation.

2.29 Non-Metathetic Reactions of Grubbs Alkene Metathesis

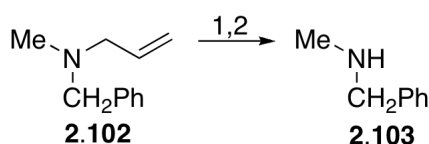
As previously noted there have been numerous non-metathetic reactions reported in the literature, Alcaide and Almendros have reported a useful summary of these reactions.⁸⁸ Snapper *et al.* reported the first non-metathetic process catalysed by the classical Grubbs' ruthenium benzylidene complex **2.17**, whilst conducting an investigation into cross metathesis observed complete chemo- and regioselective addition of chloroform across mono- and 1,1-disubstituted alkenes.⁸⁹



Reagents and Conditions: **1)** CHCl_3 , Grubbs **1**, 45°C , 2hr, 100%

Scheme 65: Grubbs I Catalysed Kharasch Reaction.

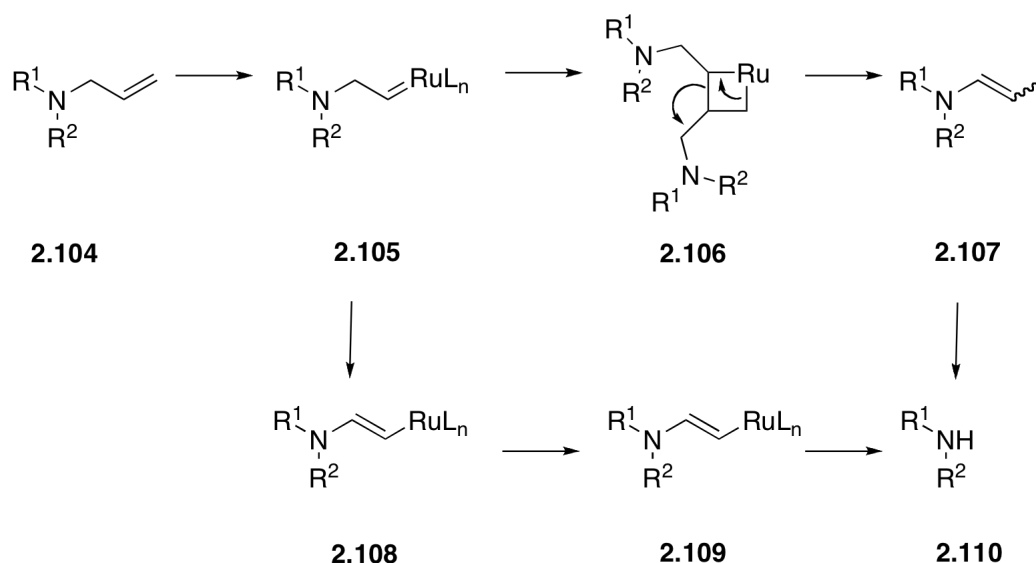
In relation to the isomerisation observed leading to compound **2.98**, it has been reported that tertiary allylamines can be readily deprotected in the presence Grubbs I **2.17**.⁹⁰



Reagents and Conditions: **1)** Grubbs **1**, PhMe , 110°C , 1.5hr,
2) SiO_2 , 78% (over 2 steps)

Scheme 66: Grubbs I Catalysed Allyl Amine Deprotection.

The mechanism of the conversion of **2.102** to **2.103** has been investigated by ^1H -NMR studies. When generic allyl amine **2.104** is treated with first generation Grubbs catalyst intermediate **2.105** is formed. Two mechanistic pathways have been proposed: the first involves an intermolecular reaction forming diamine **2.106** which collapses to reform intermediate **2.105** and enamine **2.107**, which upon treatment with silica gel degrades to secondary amine **2.110**. The alternative is identical to the mechanism proposed by Hoyer and Zhao⁷⁸ in which compound **2.105** isomerises to enamine **2.108** followed by cleavage of the ruthenium-carbon bond giving vinyl amine **2.109** which decomposed to amine **2.110** when treated with silica gel. The ^1H -NMR studies showed disappearance of the vinylic protons of **2.104** followed by appearance of an indicative methyl peak signifying that an intermediate of type **2.107** was formed.



Scheme 67: Proposed Mechanism of Deprotection

2.30 Inhibiting Non-Metathetic Reactions of Grubbs Alkene Metathesis

There have been numerous papers by several research groups reporting attempts to inhibit the non-metathetic behaviour of Grubbs catalyst by the use of various additives. Meyer and co-workers have utilised tin and iron halogenides to suppress the

isomerisation of olefins in metathesis.⁹¹ Chlorocatecholborane⁹² and 2,6-dichlorobenzoquinone⁹³ have all been used in the cross metathesis of cyclic α -methylene- β -lactones successfully inhibiting the formation of the thermodynamically favoured α,β -unsaturated lactone. Phenylphosphoric acid has also been reported as a new additive in the self-metathesis of urea-substituted alkenes, impeding isomerisation.⁹⁴

2,6-Dichlorobenzoquinone was initially chosen due to its immediate availability; although it did not arrest the formation of **2.98** it did ease purification of the product and slightly increase the yield to 70%. Chlorocatecholborane produced a similar result.

It was postulated that once the cross metathesis has occurred the pKa of the α -amino proton is decreased due the conjugation of the anion formed with the acrylamide unit, creating an electron sink which facilitates the isomerisation. Since no isomerised product was observed when an allyl amine derivative was used it was decided to revert back to this synthetic route.

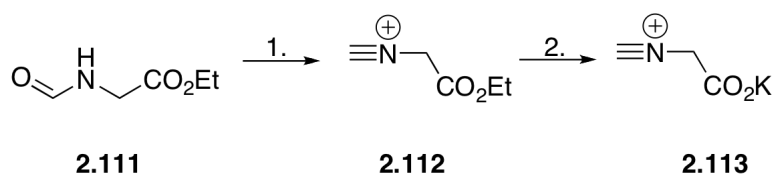
Methyl ketone **2.68** and methyl ester **2.67** were subjected to various conditions to optimise the cross metathesis. Initially methyl ester **2.67** was combined with vinyl glycine **2.16** in the presence of 10mol% of Grubbs II on a mmol scale for TLC studies, the reaction was repeated with the addition of 10mol% dichlorodicyanoquinone which by TLC showed a much cleaner reaction as observed previously when attempting to inhibit the isomerisation of **2.98**. The reaction was scaled up under these conditions.

An issue had arisen when considering the next synthetic step, obvious simply from the visual appearance of the product. This is a persistent pertinent problem associated with Grubbs catalyst: the removal of residual ruthenium from the products obtained.

2.31 Ruthenium Removal From Metathesis Products

Several research groups have made efforts to remove the remaining ruthenium. Grubbs and Maynard were first to recognise this problem using the water soluble tris(hydroxymethyl)phosphine in dichloromethane and triethylamine.⁹⁵ Unfortunately this method requires at least 86 equivalents of the expensive reagent. The use of toxic $\text{Pb}(\text{OAc})_4$ was reported in 2000.⁹⁶ Georg and co-workers have reported the use of triphenylphosphine oxide or DMSO as a viable method that suffers from the drawback of necessitating stirring 50 equivalents of reagent for 24 hours.⁹⁷ Amine-functionalized mesoporous silicates have been found to be excellent ruthenium scavengers.⁹⁸ The most recent procedure reported utilises a polar isocyanide.⁹⁹

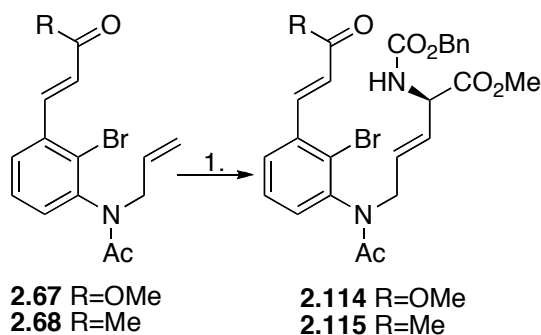
The initial choice was triphenylphosphine oxide originally due to immediate availability. It was decided to test this method of removal on the precursor to the cross metathesis recovered from the metathesis reaction. Compound **2.68** was stirred with fifty equivalents of $\text{Ph}_3\text{P}=\text{O}$ for twenty-four hours. After column chromatography there was a substantial difference in the appearance of the product going from a brown colour to translucent white. Unfortunately this method of residual ruthenium removal was not successful with the products from the cross metathesis due to similarity in R_f of both the triphenylphosphine oxide and the cross metathesis product. The next method chosen was to try to implement the polar isocyanide **2.113**, available from formate **2.111**.



Reagents and Conditions: 1) POCl₃, Et₃N, THF, -78 to 0°C, 1hr, 72%,
2) KOH, THF, rt, 5hr, 75%

Scheme 68: Synthesis of Polar Isocyanide

This method was tested on recovered starting material **2.68** and proved to be successful. The procedure was transferred to radical precursors **2.114** and **2.115** removing the residual ruthenium competently.



Reagents and Conditions: 1) See Table 5

Scheme 67

Scheme 69: Synthesis of Radical Precursor

Substrate	Reagents and Conditions	Product	Yield / %
2.67	Grubbs II (10mol%), DDQ (10mol%), CH ₂ Cl ₂ , 40°C, 18hr, then CNCO ₂ K, rt 5mins.	2.114	43
2.68	Grubbs II (10mol%), DDQ (10mol%), CH ₂ Cl ₂ , 40°C, 18hr, then CNCO ₂ K, rt 5mins.	2.115	46

Table 5: Results for the Formation of 2.114 and 2.115.

Finally with the desired radical precursors in hand our attention was turned to the radical cyclisation.

2.32 Executing Radical Reactions

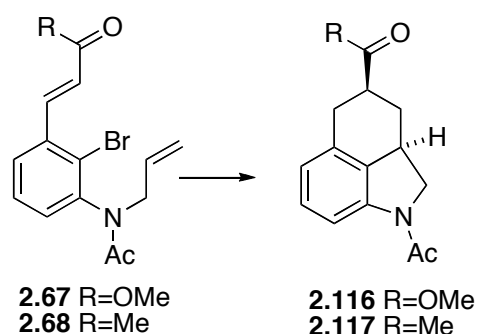
When undertaking a radical reaction several factors must be taken into consideration.

Using highly dilute solutions ca. 0.01M inhibits intermolecular reactions leading to polymeric species. The elimination of radical acceptors and therefore terminators of the required reaction from the reaction medium is essential, to accomplish this solvents must be degassed prior to the reaction by the freeze-thaw method and purged with nitrogen. Additionally suba-seals should be used with caution; they should never come into contact with refluxing solvents, so in this instance should only be inserted at the top of the reflux condenser. The concentration of tributyltin radicals at anytime is a pertinent issue, ideally this would be constant throughout the reaction. Current methods to achieve this scenario are either the use of a syringe pump to add a solution of AIBN and Bu_3SnH slowly at a rate that is consistent with the reaction rate, or the use of a reductive catalytic system.

The reductive catalytic method was first utilised in a cascade sequence by Stork *et al.*¹⁰⁰ A publication by Kuivila and Menapace noting the reduction of alkyl halides in the presence of lithium aluminium hydride and alkyl tin halides,¹⁰¹ incited Corey and co-workers to develop the milder procedure, due to their interest in prostaglandin synthesis, to reductively dehalogenate an advanced intermediate.¹⁰²

2.33 Synthesis of Model Tricycles

In order to gain familiarity and to compare the effectiveness of the procedures, the radical reactions were tested on methyl ester **2.67** and methyl ketone **2.68**.



Reagents and Conditions: 1) See Table 6

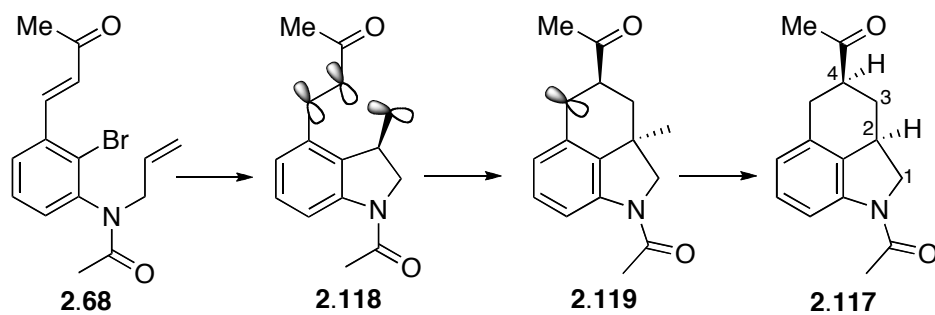
Scheme 70: Synthesis of Test Tricycles

Substrate	Reagents and Conditions	Product	Yield/ %
2.67	SnBu ₃ Cl (0.1eq), NaCNBH ₃ (2eq), AIBN, ^t BuOH, 80°C, 18hr.	2.116	56
2.67	SnBu ₃ H, AIBN, PhMe, 110°C, 18hr.	2.116	71
2.68	SnBu ₃ Cl (0.1eq), NaCNBH ₃ (2eq), AIBN, ^t BuOH, 80°C, 18hr.	2.117	53
2.68	SnBu ₃ H, AIBN, PhMe, 110°C, 18hr.	2.117	73

Table 6: Results of Model Studies.

Examination of molecular models indicates the most likely relative stereochemistry of H-2 and H-4 is *cis*. The relative stereochemistry represented above can be rationalised by the mechanism delineated below. Once the first cyclisation has occurred it can be said that the hydrogen of **2.118** is pointing down. Consequently, once the subsequent cyclisation occurs, the primary radical of the methyl group is pointing up, attacking from above maintaining maximum p-orbital overlap and H-4 is forced down. The

resulting benzyl radical is quenched to give the *cis* indloine **2.117**. This deduction is supported by $^1\text{H-NMR}$, the pseudo quartet at δ 1.49 ppm is typical of systems with H-2, H-4 *cis* stereochemistry.^{103,104}



Scheme 71: Rationale of Proposed Relative Stereochemistry.

2.34 Discussion of ^1H -NMR data of 2.116 and 2.117

The ^1H -NMR of the methyl ester analog 2.116 is pictured below.

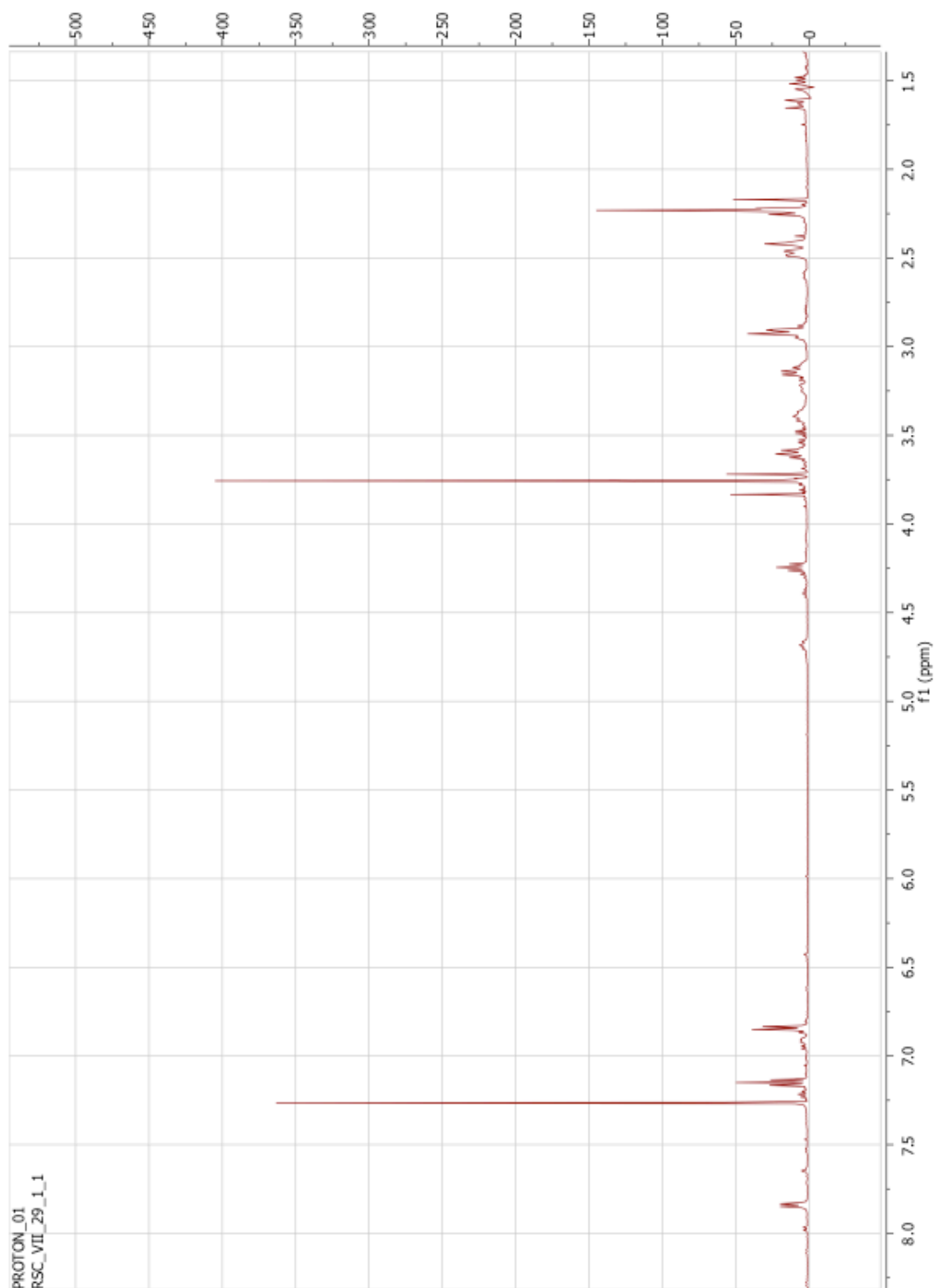


Figure 7: The ^1H -NMR spectrum of 2.116.

The ^1H -NMR of the methyl ketone analog **2.117** is pictured below.

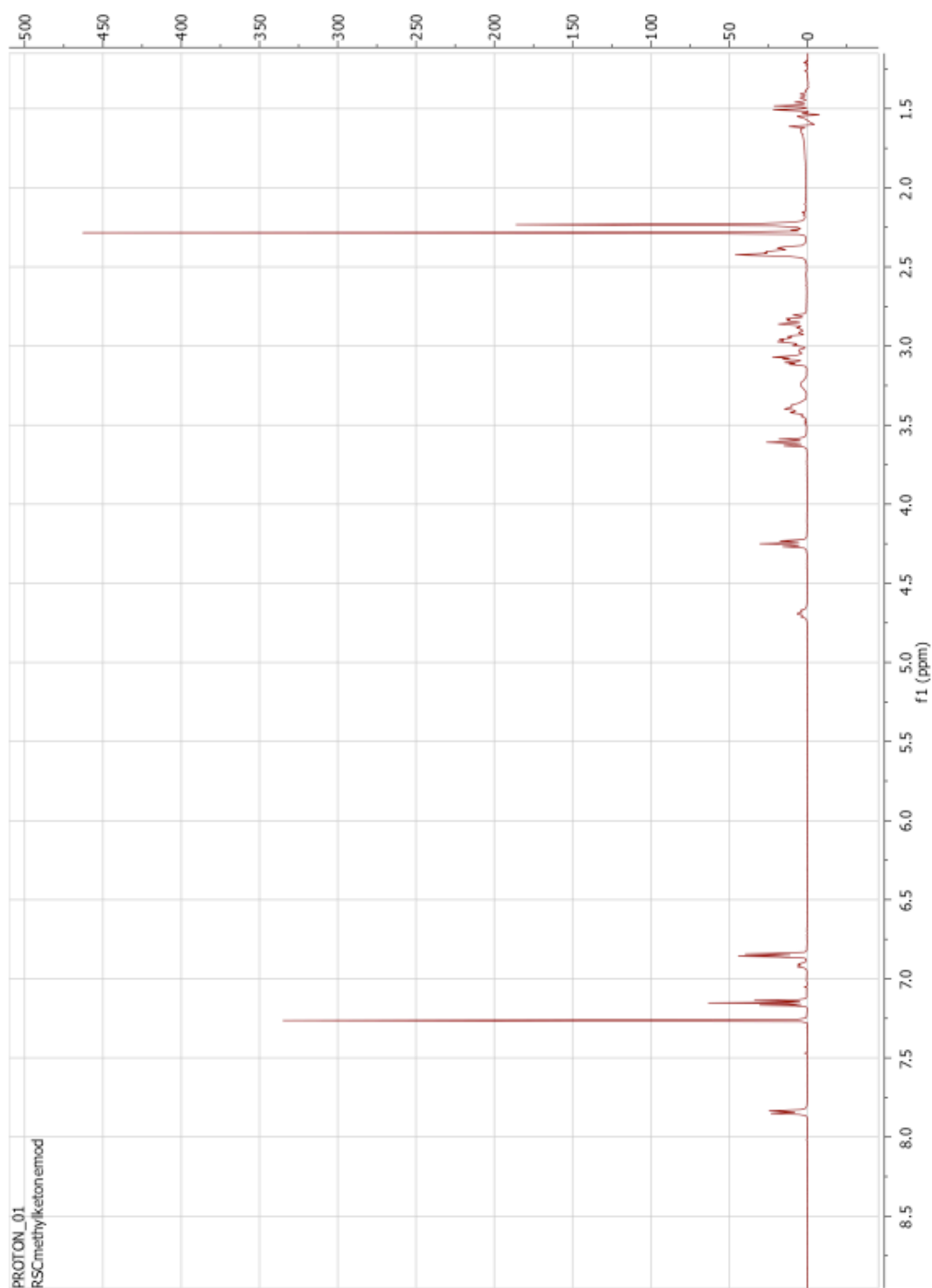


Figure 8: The ^1H -NMR spectrum of **2.117**.

Proton	Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)
H-1 α	4.25	t'	9.2
H-1 β	3.61	t'	10.5
H-2 β	3.25	m	
H-3 α	1.49	q'	11.7
H-3 β	2.4	dd	12.2, 9.2
H-4 β	3.41	dd	11.7, 11.4
H-5 α	2.83	dd	16.7, 11.4
H-5 β	3.09	dd	16.7, 6.1

Table 7: NMR data of 2.117

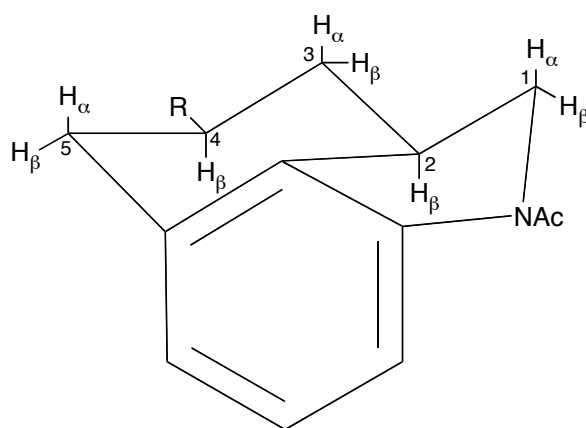


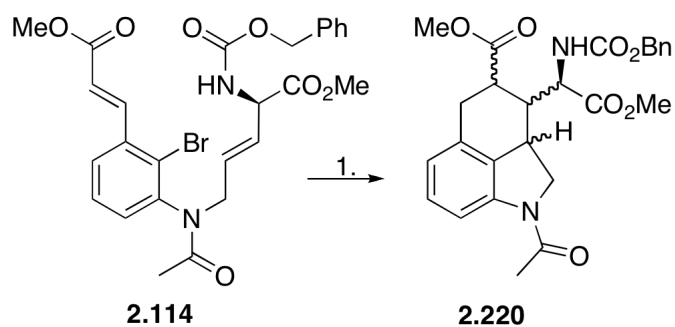
Figure 9: Conformer of 2.117.

The data extracted from the ^1H -NMR of **2.117** is summarised in the table above and **2.117** drawn in the conformer above helps explain this data. The signals for both H-1 α and H-1 β appear as pseudo triplets at 4.25 and 3.61ppm respectively, it would be expected that they would both appear as a doublet of doublets; for H-1 α due to the geminal coupling between H-1 α and H-1 β and an axial-axial vicinal coupling between H-1 α and H-2 β . H-1 β has the same geminal coupling between H-1 α and H-1 β and an axial-equatorial vicinal coupling between H-1 β and H-2 β . H-2 β appears as an unresolved multiplet at 3.25ppm. H-3 α is a pseudo-quartet ($J=11.7\text{Hz}$) at 1.49ppm this is due to two axial-axial vicinal couplings between H-3 α and H-2 β plus H-3 α and H-4 β , in addition to the geminal coupling between H-3 α and H-3 β . H-3 β signal has been resolved as a doublets of doublets ($J=12.2$ and 9.2Hz) the

coupling constant of 12.2Hz for the geminal coupling between H-3 α and H-3 β . H-3 β should also couple with both H-2 β and H-4 β in an axial-equatorial vicinal manner. The coupling constant observed of 9.2Hz is for one of these. H-4 β signal 3.41ppm has been resolved as a doublet of doublets of doublets ($J=11.7$, 11.4 and 6.1Hz), The coupling constant observed of 11.7Hz is for the axial-axial vicinal coupling between H-3 α and H-4 β and the coupling constant observed of 11.4Hz is for the axial-axial vicinal coupling between H-5 α and H-4 β , the coupling constant of 6.1Hz is from an axial-equatorial vicinal coupling between H-4 β and H-5 β . H-5 α appears as a doublet of doublets ($J=16.7$ and 11.4Hz) at 2.83ppm, the large coupling constant of 16.7Hz is a result from the geminal coupling between H-5 α and H-5 β . The coupling constant observed of 11.4Hz is for the axial-axial vicinal coupling between H-5 α and H-4 β . H-5 β appears as a doublet of doublets ($J=16.7$ and 6.1Hz), as discussed the coupling constant of 16.7Hz is for geminal coupling between H-5 α and H-5 β . The smaller coupling constant of 6.1Hz is from an axial-equatorial vicinal coupling between H-4 β and H-5 β . This data is consistent with the diastereoisomer displayed.

2.35 Synthesis of Amide Analogue

On the basis of the results obtained it was decided that slow addition of a tributyltin hydride solution *via* a syringe pump would be the method implemented on substrates **2.114** and **2.115**. Unfortunately **2.115** gave an inseparable multi-spot component mixture, however methyl ester **2.114** gave 74%, based on recovered starting material, of a diastereomeric mixture of **2.220**. TLC analysis showed four compounds.



Reagents and Conditions: 1) TBTH, AIBN, PhMe, 110°C, 74%

Scheme 72: Synthesis of Key Tricyclic

Unfortunately the products obtained from the reaction were very difficult to purify, although TLC analysis would show a retention factor of 0.22 when 10% $\text{NH}_4\text{OH}/\text{MeOH}:\text{CH}_2\text{Cl}_2$ (1:99) was used, if this solution was used to elute a column for flash chromatography it would result in all of the products flushing out in under five tubes. Subsequently the column was eluted with (1:200), which by TLC analysis showed no movement of the substrate from the baseline, allowed for a partial separation of the diastereoisomers. The product was subjected to several purifications by chromatography, however all attempts were futile in attempting to isolating the individual diastereoisomers, the gradual loss of product in attempts to purify led to exploring an alternative approach.

2.36: Discussion of ^1H -NMR data of 2.220

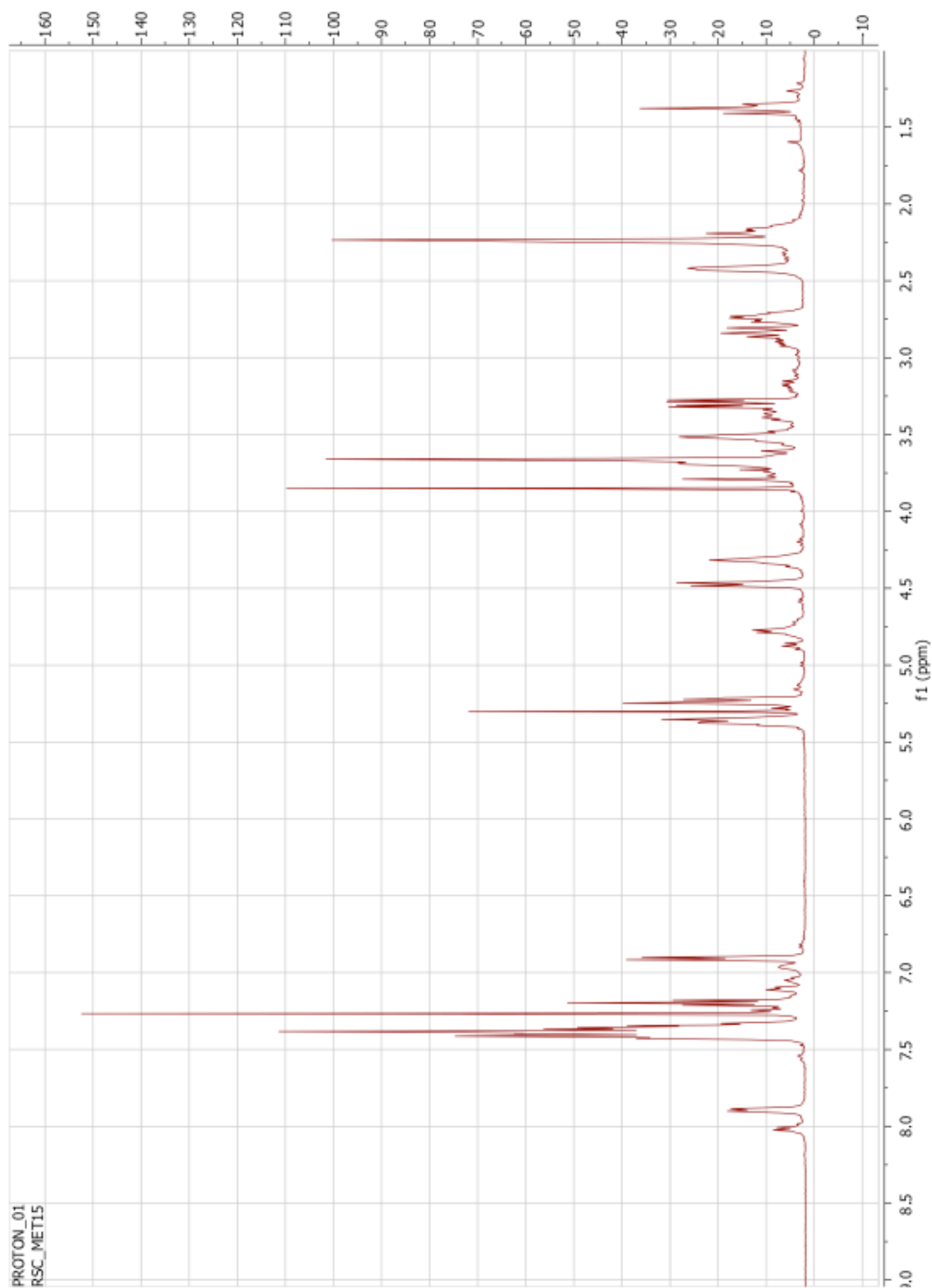


Figure 8: ^1H -NMR of 2.220

The ^1H -NMR of **2.220** is far more difficult to interpret than the spectra of **2.117**. It does indicatively show that olefinic signals have disappeared. The two sets of

doublets previously recorded at 8.06 and 6.40ppm and the multiplet and doublet observed at 5.84 and 5.51ppm respectively are also absent.

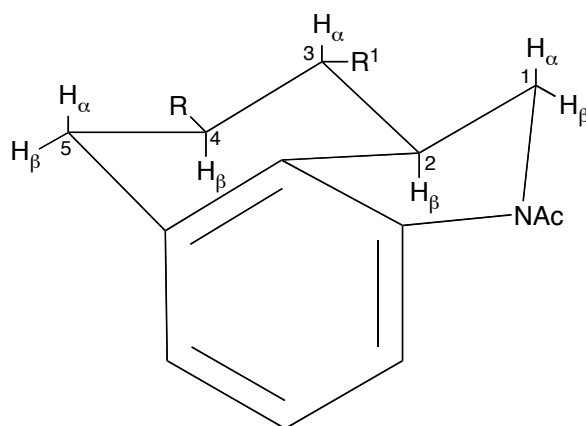
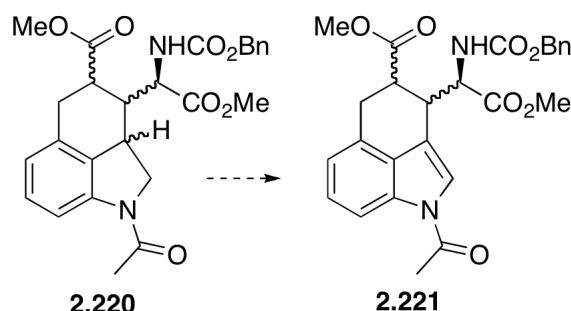


Figure 10: Proposed Diastereoisomer of **2.220**

A proportion of the signals observed from the ^1H -NMR of **2.220** do give some information about one of the possible diastereoisomers produced, delineated above in **Figure 9**: A triplet of doublets ($J=11.9$ and 5.6Hz) is observed at 2.74ppm , this signal could be attributed to $\text{H-3}\alpha$, with two similar axial-axial vicinal couplings between $\text{H-3}\alpha$ and $\text{H-2}\beta$ plus $\text{H-3}\alpha$ and $\text{H-4}\beta$ producing the triplet and the doublet from coupling with the proton of the amino acid side chain. A doublet of doublets (16.9 and 11.8Hz) at 2.82ppm , a similar signal observed in ^1H -NMR spectrum of **2.117**, can be attributed to $\text{H-5}\alpha$. The coupling constant of 16.9Hz is a result from the geminal coupling between $\text{H-5}\alpha$ and $\text{H-5}\beta$. The coupling constant observed of 11.8Hz is for the axial-axial vicinal coupling between $\text{H-5}\alpha$ and $\text{H-4}\beta$. A doublet of doublets (16.9 and 5.9Hz) at 3.30ppm is assigned to $\text{H-5}\beta$, the coupling constant of 16.9Hz is for geminal coupling between $\text{H-5}\alpha$ and $\text{H-5}\beta$. The smaller coupling constant of 5.9Hz is from an axial-equatorial vicinal coupling between $\text{H-4}\beta$ and $\text{H-5}\beta$. This data indicates the diastereoisomer displayed above, although more extensive NMR studies need to be conducted.

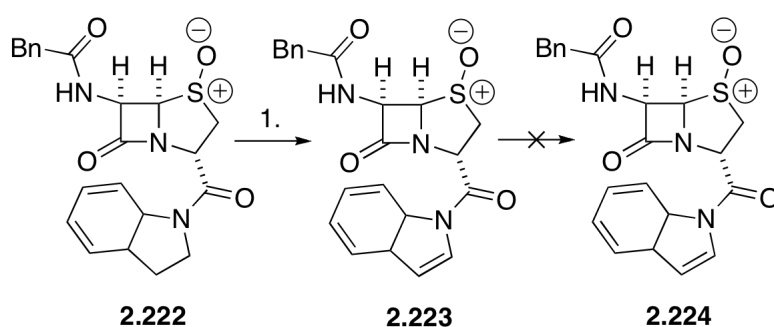
2.37 Attempted Oxidation of Amide Analogue

It was decided that it could be possible to simplify the situation if one of the stereogenic centres was removed by the oxidation of indoline **2.220** to indole **2.221**.



Scheme 73: Oxidation of Indoline **2.220**

Research of the literature disclosed several suitable protocols. The desired transformation was initially used by Barrett and co-workers at Imperial college, London, who developed the concept of latent aromaticity.¹⁰⁵ Barrett *et al.* used DDQ as mild oxidant of advanced penicillin intermediate **2.222**. However model studies on simpler systems, in respect of regenerating the dormant acid, indicated that the basic conditions required for the deprotection were not compatible with the real system.



Reagents and Conditions: 1) Dichlorodicyanobenzoquinone, CH₂Cl₂

Scheme 74: DDQ oxidation

This idea has been extended and applied in the total synthesis of the complex CP molecules by Nicolaou and Co-workers.¹⁰⁶ Impressively the protection group was

implemented in the total synthesis of CP-255,915 and CP-263,114, allowing the protection of a highly developed intermediate. Following intense investigation it was found that *p*-chloroanil was the most successful reagent in promoting the desired transformation, and hence realising the totynthesis of this notable target.

The use of manganese(III)acetate in acetic acid has been reported by Ketcha.¹⁰⁷ The harsh conditions required to promote the reaction were deemed inappropriate for substrate **2.220** when considering the complex nature of the starting material.

DDQ and *p*-chloroanil were tested on substrate **2.220**; unfortunately neither reaction was capable of effecting the transformation.

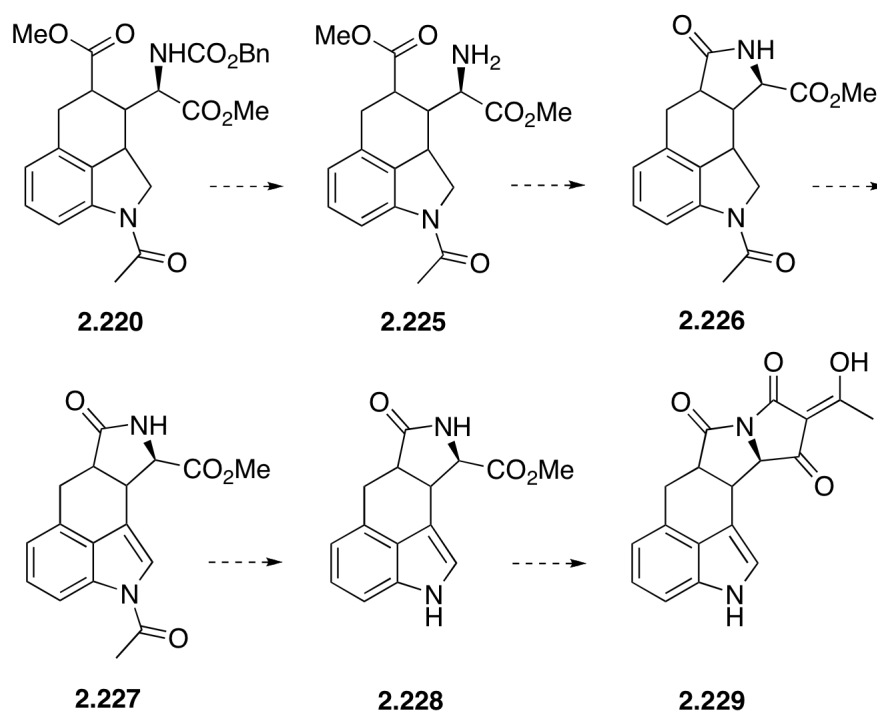
Future Work

2.38 Completing of Amide Analogue of α -CPA

Completion of the project, in respect to the current route, could multitple directions.

There are four transformations required to complete the synthesis of the amide analog.

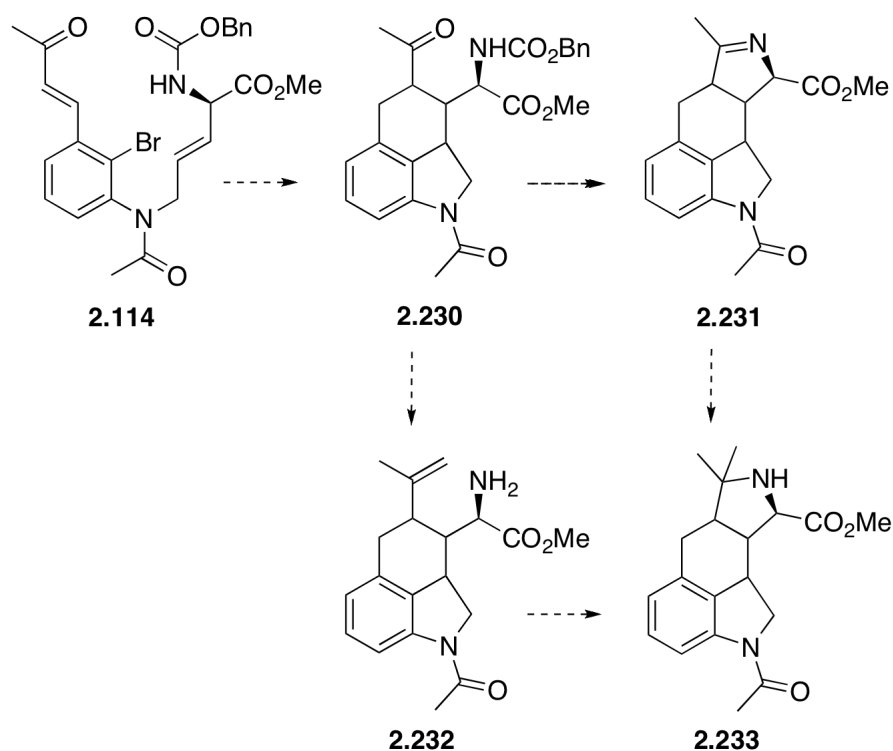
Firstly the deprotection of the benzyl carbamate, typically achieved with H₂/Pd-C in MeOH,^{108 109} alternatively Me₃SiI in acetonitrile¹¹⁰ or triethylsilane in ethanol with a catalytic amount of triethylamine¹¹¹ and Pd(OAc)₂.¹¹² This would be followed secondly by condensation of the newly formed primary amine with the proximal ester moiety possibly assisted by Lewis acid catalysis. Thirdly the indoline functionality could be oxidised to an indole using one of the methods previously discussed; subsequent deprotection of the acetamide functionality is necessary. The order of these steps could be altered. Once amide **2.228** is obtained the synthesis will follow the same sequence as previously published.



Scheme 75: Steps Required for the Completion of Amide Analogue of α -CPA **1.01**

2.39 Completing the Total Synthesis of α -CPA

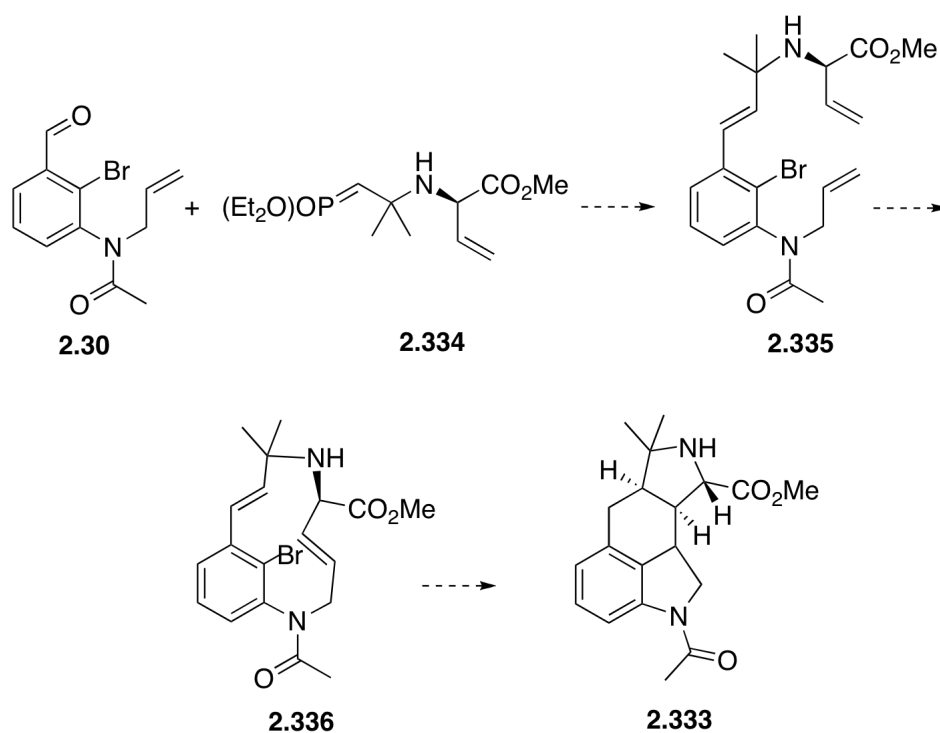
To complete the synthesis of α -CPA **1.01** it is necessary to optimise the radical cyclisation of methyl ketone **2.115** to tricycle **2.230**. Two approaches are envisaged: deprotection of the amine followed by condensation with ketone to form imine **2.231** an intermediate that is an indoline version of **1.36**. Addition of a methyl anion to ketimine **2.231** will furnish intermediate **2.233**, that could be subjected a similar sequence to that outlined for **2.229**. Alternatively **2.230** could be transformed to **2.232**, through a Wittig reaction, which upon exposure to acid will cyclise *via* a tertiary cation to **2.233**.



Scheme 76: Future work for the Total Synthesis of a-CPA **1.01**

2.40 Macrocyclic Radical Cascade Approach to α -CPA

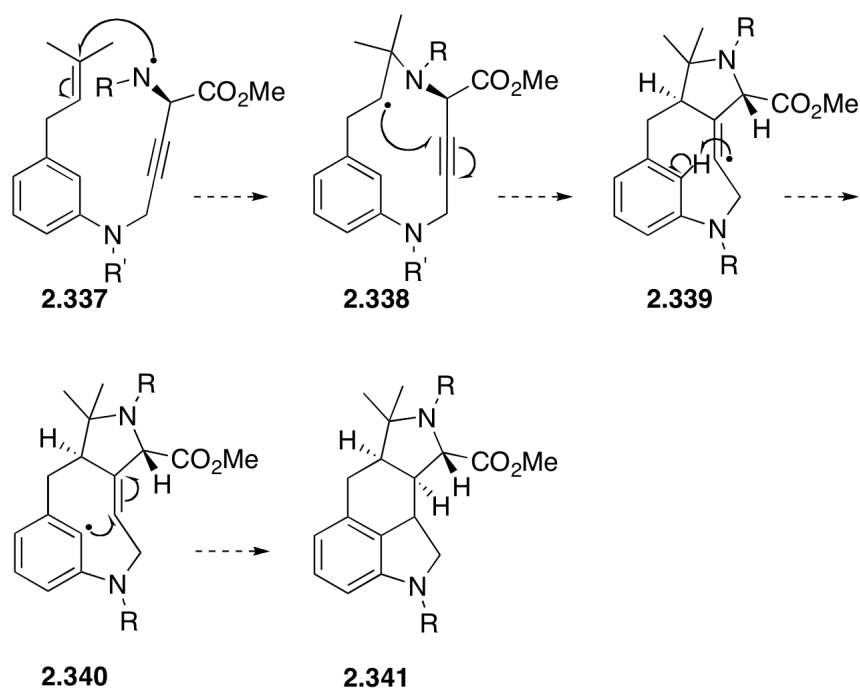
When considering the diastereomeric mixture obtained from the radical cascade of **2.114**, an alternative complimentary route could be investigated. Utilising previously synthesised aldehyde **2.30** in a Horner-Wadworth-Emmons reaction with **2.334**, which can be derived from vinyl glycine, would give triene **2.335**. Subjecting **2.335** to Grubbs catalyst will provide macrocycle **2.336**. The asymmetrically constrained transition state would yield the desired precursor, through a transannular cyclisation, in a homochiral form.



Scheme 77: A Transmolecular Cylisation Approach to α -CPA **1.01**

2.41 A New Approach to α -CPA

A final approach to α -CPA **1.01** has been designed. If intermediate **2.337** was synthesised, treatment with NCS followed by addition of SnBu_3H would yield a nitrogen radical that would spontaneously macrocyclise onto the alkene. Subsequent reaction of the secondary radical **2.338** onto the alkyne would give alkenic radical **2.339**. H-abstraction followed by cyclisation would yield advanced tetracycle **2.341**.



Scheme 78: A New Approach to a-CPA **1.01**

2.42 Conclusion

Thorough investigation has developed a successful route to the desired radical precursor. The proposed radical cascade has been tested and proved successful on a potential amide analogue of a-CPA **1.01**; however, the diastereomeric mixture obtained may indicate a different direction may have to be pursued. The macrocyclic transmolecular approach outlined in **Scheme 77** should be explored since it would solve the diastereomeric dilemma.

Experimental

3.1 General Procedure

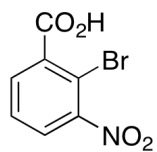
Reactions were conducted at room temperature under an atmosphere of nitrogen unless otherwise stated. Reactions were monitored using analytical thin-layer chromatography with visualisation by UV light and either alkaline potassium permanganate (KMnO₄), vanillin, or phosphomolybdic acid (PMA) dips.

Reaction solvents were purified and dried according to literature methods. THF and diethyl ether were distilled from sodium with benzophenone as an indicator, CH₂Cl₂ and acetonitrile were distilled from CaH₂. The use of hexanes refers to distilled petroleum 40-60°C. All other solvents and reagents were used as supplied. Flash chromatography was performed using silica gel 60, 230-400 mesh.

¹H NMR spectra were recorded on a Bruker 300MHz or a Varian 500MHz machine (operating at ambient probe temperature using an internal deuterium lock). Chemical shifts were reported in parts per million (ppm), using residual solvent as an internal standard. Standard abbreviations were used throughout (s singlet; bs broad singlet; d doublet; dd doublet of doublets; dt doublet of triplets; dq doublet of quartets; t triplet; q quartet; m multiplet). Coupling constants were measured in Hertz (Hz). ¹³C NMR spectra were recorded at 126 MHz. Chemical shifts are reported in parts per million (ppm); m, M or m/M denotes either the major or minor diastereomer (or both as a combined signal).

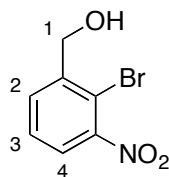
ESI Mass spectra were recorded on a Bruker Daltonics Apex III spectrometer with methanol as solvent. EI mass spectra were recorded on a Fisons VG Autospec spectrometer. Infra red spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer. Alpha-D were recorded on a AUTOPOL IV Polarimeter at an ambient temperature of 23°C.

2.06: 2-Bromo-3-nitrobenzoic acid



The title compound was prepared using the method Culhane *et al.*⁵² (52.12g, 74%)

2.07: 2-Bromo-3-nitrobenzyl alcohol

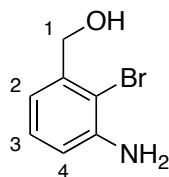


To a stirring solution of 2-bromo-3-nitrobenzoic acid **2.06** (51.32g, 209mmol) in THF 200ml at 0°C to this a solution of BH₃.THF (1.0M, 418ml, 418mmol) was added dropwise maintaining the temperature below 2°C. Once addition was complete the solution was stirred for an hour at 0°C and then allowed to warm to room temperature. The solution was added to ice in water (200ml) followed by addition of K₂CO₃ until saturated. The organic layer was separated and the aqueous phase was washed with Et₂O (3x100ml). The organic extracts were combined and the solvent was removed under reduced pressure. The crude extract was purified by column chromatography (PE:Et₂O, 3:2) to give 2-bromo-3-nitrobenzyl alcohol **2.07** (44.05g, 91%) as a white solid.

¹H NMR (300 MHz, CDCl₃) δ: 7.61 (d, J = 7.1, 1H, H-4), 7.47 (d, J = 8.00, 1H, H-2), 7.32 (t, J = 7.84, 1H, H-3), 4.65 (s, 2H, H-4), 2.05 (s, 1H, OH).

Physical properties and spectra comparable to that reported in the literature.^{25, 26, 27}

2.03: 3-Amino-2-bromobenzyl alcohol

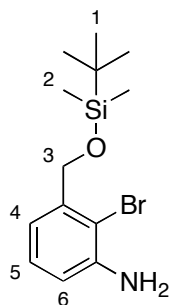


Iron powder (5.58g, 0.1mol) was added to a stirring solution of 2-bromo-3-nitrobenzyl alcohol **2.07** (5.32g, 22.9mmol) in glacial acetic acid (70ml) and absolute ethanol (70ml) and the mixture was refluxed for 3 hours. The mixture was allowed to cool to room temperature upon which water (100ml) was added and the solvents from the mixture were removed under reduced pressure. The mixture was washed with ethyl acetate (3x100ml), the combined extracts were washed with saturated sodium bicarbonate, dried with magnesium sulphate and the solvent was removed under reduced pressure. The crude extract was purified using column chromatography to give 3-amino-2-bromobenzyl alcohol **2.03** (3.47g, 75%) as a white solid.

^1H NMR (300 MHz, CDCl_3) δ : 7.04 (t, $J = 7.79$, 1H, H-3), 6.81 (d, $J = 7.1$, 1H, H-4), 6.43 (d, $J = 8.00$, 1H, H-2), 4.57 (s, 2H, H-4), 2.84 (s, 2H, NH), 2.15 (s, 1H, OH).

Physical properties and spectra comparable to that reported in the literature.^{25, 26, 27}

2.08: 2-Bromo-3-(*tert*-butyldimethylsilyloxymethyl)aniline.

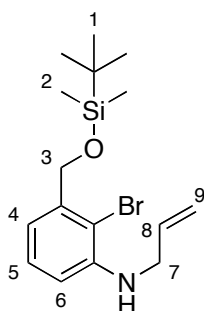


To a stirring solution of 3-amino-2-bromobenzyl alcohol **2.03** (3.22g, 15.9mmol) imidazole (1.62g, 23.9mmol) and a catalytic amount of DMAP in anhydrous DMF (15ml) was cooled in an ice bath to 0°C. Once the mixture was homogeneous, *tert*-butyldimethylsilylchloride (2.80, 18.6mmol) was added. The mixture was allowed to warm to room temperature and was allowed to stir for 18 hours. A saturated brine (15ml) solution was added to the mixture and the mixture was extracted with Et₂O (3x15ml) and the combined extracts were dried with magnesium sulphate. The solvent was removed under reduced pressure to give a yellow oil. The crude extract was purified using column chromatography (PE:Et₂O, 4:1) to give 2-bromo-3-(*tert*-butyldimethylsilyloxymethyl)aniline **2.08** (4.63g, 92%) as a light yellow oil.

¹H NMR (300 MHz, CDCl₃) δ: 7.12 (t, J = 7.84, 1H, H-5), 6.87 (d, J = 7.15, 1H, H-4), 6.49 (d, J = 7.98, 1H, H-6), 4.59 (s, 2H, H-3), 3.76 (s, 2H, NH), 0.95 (s, 9H, H-1), 0.06 (s, 6H, H-2).

Physical properties and spectra comparable to that reported in the literature.^{25, 26, 27}

2.09: 3-(N-Acetyl-N-allylamino)-2-bromobenzyl alcohol

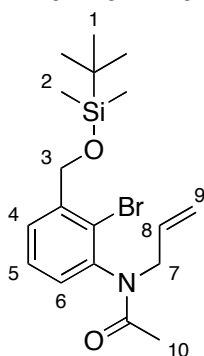


A solution of LDA was freshly prepared from diisopropylamine (0.73ml, 5.21mmol) and *n*-butyllithium (1.0M, 3.67ml, 3.67mmol) in anhydrous THF (20ml) at 0°C was added dropwise *via* cannula to a stirring solution of 2-bromo-3-(*tert*-butyldimethylsilyloxymethyl)aniline **2.08** (1.00g 3.16mmol) in anhydrous THF (50ml) at -78°C under a nitrogen atmosphere. The solution was allowed to warm to room temperature upon which a yellow solution formed. The solution was again cooled to -78°C and allyl bromide (0.29ml, 3.37mmol) was added dropwise. Once addition was complete the solution was allowed to warm to room temperature and was stirred for a further 3 hours. A saturated ammonium chloride solution (50ml) was added and the organic layer was separated. The aqueous extract was washed with Et₂O (3x30ml) and the combined extracts were dried with magnesium sulphate. The solvent was removed under reduced pressure. The crude extract was purified by column chromatography eluted with (PE:Et₂O, 95:5), to give 3-(N-acetyl-N-allylamino)-2-bromobenzyl alcohol **2.09** (0.81g, 72%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃) δ 7.18 (t, J = 7.79, 1H, H-5), 6.92 (d, J = 7.05, 1H, H-6), 6.81 (d, J = 7.91, 1H, H-4), 5.91 (m, 1H, H-8), 5.30 (d, J = 17.0, 1H, H-9E), 5.13 (d, J = 10.7, 1H, H-9Z), 4.67 (s, 2H, H-3), 3.79 (m, 2H, H-13) 2.65 (s, 1H, NH), 0.92 (s, 9H, H-1), 0.06 (s, 6H, H-2).

Physical properties and spectra comparable to that reported in the literature.^{25, 26, 27}

2.10: 2-Bromo-3-(*tert*-butyldimethylsilyloxymethyl)-N-acetyl-N-allylaniline.

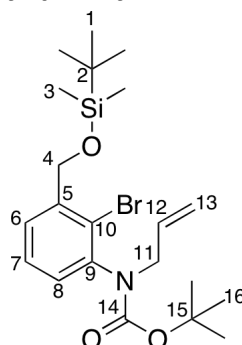


A solution of LDA was freshly prepared from diisopropylamine (0.73ml, 5.21mmol) and *n*-butyllithium (1.0M, 3.67ml, 3.67mmol) in anhydrous THF (20ml) at 0°C was added dropwise *via* cannula to a stirring solution of **2.08** 2-bromo-3-(*tert*-butyldimethylsilyloxymethyl)aniline (1.00g 3.16mmol) in anhydrous THF (50ml) at -78°C under a nitrogen atmosphere. The solution was allowed to warm to room temperature upon which a yellow solution formed. The solution was again cooled to -78°C and allyl bromide (0.29ml, 3.37mmol) was added dropwise. Once addition was complete the solution was allowed to warm to room temperature and was stirred for a further 3 hours. A saturated ammonium chloride solution (50ml) was added and the organic layer was separated. The aqueous extract was washed with Et₂O (3x30ml) and the combined extracts were dried with magnesium sulphate. The solvent was removed under reduced pressure. The crude product was dissolved in anhydrous THF (40ml). Freshly distilled acetyl chloride (0.90ml, 12.6mmol) was added and the solution was stirred at room temperature for an hour. The solution was quenched with saturated sodium bicarbonate solution (40ml), the organic layer was separated and the aqueous extract was washed with ethyl acetate (3x50ml). The organic layers were combined, dried with magnesium sulphate and the solvent was removed under reduced pressure. The crude extract was purified by column chromatography (PE:Et₂O, 1:1) to give **2.10** 2-bromo-3-(*tert*-butyldimethylsilyloxymethyl)-N-acetyl-N-allylaniline (1.03g, 82%) as a yellow oil.

¹H NMR (300 MHz, CDCl₃) δ: 7.59 (t, *J* = 7.8, 1H, H-7), 7.08 (d, *J* = 7.13, 1H, H-4), 6.90 (d, *J* = 7.94, 1H, H-6), 5.88 (m, 1H, H-8), 5.27 (d, *J* = 16.9, 1H, H-9*E*), 5.15 (d, *J* = 11.0 1H, H-9*Z*), 4.78 (s, 2H, H-4), 4.10 (m, 2H, H-7), 1.79 (s, 3H, H-10) 0.97 (s, 9H, H-1), 0.04 (s, 6H, H-3).

Physical properties and spectra comparable to that reported in the literature.^{25, 26, 27}

2.11: *Tert*-butyl allyl[2-bromo-3-({*tert*-butyl(dimethyl)silyl}oxy)methyl]phenyl]carbamate



2-Bromo-3-({*tert*-butyl(dimethyl)silyl}oxy)methyl)aniline (1.759g, 5.58mmol) was dissolved in THF (40ml) and cooled to -78°C under a nitrogen atmosphere. In a separate flask THF (10ml) was charged with nitrogen and DIPA (1.30ml, 9.21mmol) was added. The solution was cooled to -10°C . $n\text{-BuLi}$ (2.2M in hexanes, 2.54ml, 5.58mmol) was added dropwise, maintaining the temperature below -5°C . The solution was stirred for 10 minutes. The freshly formed LDA was added dropwise *via* cannula to the stirring solution of the aniline maintaining the temperature below -75°C . Once all the LDA had been added the mixture was allowed to slowly warm to 0°C . The yellow solution was cooled to -78°C . Freshly distilled allyl bromide (0.67g, 5.97mmol) was added dropwise, maintaining the temperature below -75°C . The solution was allowed to warm to room temperature. Saturated aqueous NH_4Cl solution (30ml) was added and the organic layer was isolated. The remaining aqueous layer was washed with Et_2O (3x30ml). The organic fractions were combined, dried with anhydrous MgSO_4 and the solvent was removed under reduced pressure. The crude extract was dissolved in acetonitrile (50ml) and cooled to 0°C under a nitrogen atmosphere. NEt_3 (1.57ml, 11.2mmol) and DMAP (cat.) were added. In a separate flask Boc_2O (2.44g, 11.2mmol) was dissolved in acetonitrile (10ml) under a nitrogen atmosphere. The solution was added dropwise *via* cannula to the previously prepared solution (effervescence!). The solution was allowed to warm to room temperature and allowed to stir for 2hr. The solvent was removed under reduced pressure. Deionized water (40ml) was added to the crude extract and washed with Et_2O (3x40ml). The combined organic layers were combined and washed with saturated aqueous NH_4Cl solution (30ml). The organic phase was dried MgSO_4 and the solvent was removed under reduced pressure. The crude extract was dissolved in a minimal amount of hexanes and loaded onto a prepacked column. The column was eluted with (PE: Et_2O , 95:5), *tert*-butyl allyl[2-bromo-3-({*tert*-butyl(dimethyl)silyl}oxy)methyl]phenyl]carbamate was isolated as a colourless oil (2.25g, 88%). $R_f = 0.28$ (PE: Et_2O , 95:5).

m/z (EI $^{+}$): 480, 459, 400, 318, 241, 172, 141

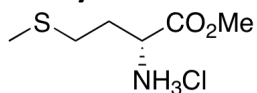
HRMS (ESI): Calcd. for $\text{C}_{21}\text{H}_{34}\text{BrNO}_3\text{Si}$ $[\text{M}+\text{Na}]^{+}$: 478.1384; found: 478.1387

^1H NMR (300 MHz, CDCl_3) δ 7.04 (t, $J = 7.84$, 1H, H-7), 6.81 (d, $J = 7.1$, 1H, H-8), 6.43 (d, $J = 8.00$, 1H, H-6), 5.82 (m, 1H, H-12), 5.15 (d, $J = 17.2$, 1H, H-13E), 5.08 (d, $J = 10.8$, 1H, H-13Z), 4.57 (s, 2H, H-4), 3.64 (m, 2H, H-11), 1.39 (s, 9H, H-16), 0.97 (s, 9H, H-1), 0.04 (s, 6H, H-3).

^{13}C NMR (126 MHz, CDCl_3) δ : 147.21, 145.03, 135.09, 127.83, 116.92, 116.14, 110.78, 108.46, 85.14, 65.44, 46.87, 27.48, 26.43, 18.92, -5.023.

ν_{max} (film/ cm^{-1}): 2929, 1810, 1706, 1596, 1470, 1367.

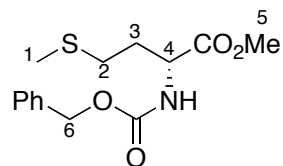
2.13: *D*-Methionine methyl ester hydrochloride.



2.12 *D*-Methionine (20.2g, 0.135mol) was suspended in 2,2-dimethoxypropane (500ml), 36% aqueous HCl (50ml) was added slowly, followed by dropwise addition of MeOH (ca. 10ml) until complete dissolution. The solution was allowed to stir for 18 hours during which it had turned a dark red colour. The solvent was removed under reduced pressure to produce a very dark red sludge. This was dissolved in a minimal amount of MeOH (ca. 30ml) and transferred to a dropping funnel. Et₂O (1000ml) was placed in a 2L conical flask equipped with a magnetic stirrer. The methanolic solution was added dropwise to the stirring Et₂O. After complete addition the mixture was poured through a Buchner funnel, an off-white solid was collected and dissolved in a minimal amount of MeOH (ca. 20ml) and the crystallisation process was repeated to produce **2.13** *D*-methionine methyl ester hydrochloride as a white solid (25.14g, 93%).

Physical properties and spectra comparable to that reported in the literature.⁴⁸

2.14: *N*-[(Benzyloxy)carbonyl]-*D*-methionine methyl ester.

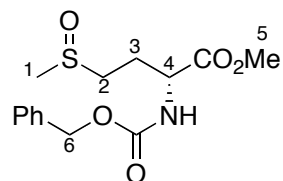


To an ice cold solution of **2.13** *D*-Methionine methyl ester hydrochloride (24.13g, 0.121mol) and potassium bicarbonate (60g) in deionised water (500ml) and EtOAc (500ml) was added dropwise benzyl chloroformate (22.71, 0.133mol) over an hour period. The biphasic mixture was stirred for a further 4 hours. The organic layer was separated, the aqueous phase was washed with EtOAc (2x100ml) and organic phases were combined, washed with 1M HCl (400ml) and then with water (400ml). The solvent was dried with MgSO₄ and removed under reduced pressure to give a colourless oil. The crude product was purified by column chromatography (PE, Et₂O, 1:1) followed by crystallisation from PE to give **2.14** *N*-[(benzyloxy)carbonyl]-*D*-methionine methyl ester (30.13g, 88%) as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 7.36 (m, 5H, Ar-H), 5.89 (s, 1H, NH), 5.08 (s, 2H, H-6), 4.25 (m, 1H, H-4), 3.69 (s, 3H, H-5), 2.42 (m, 2H, H-2), 2.20 (m, 2H, H-3), 1.88 (s, 3H, H-1)

Physical properties and spectra comparable to that reported in the literature.⁴⁸

2.15: Methyl *D*-2-[[[(benzyloxy)carbonyl]amino]-4-(methylsulfinyl)butanoate.

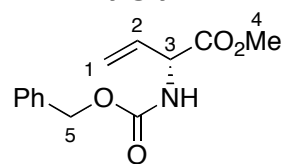


To an ice cold stirring solution of sodium metaperiodate (22.74g, 0.106mol) in water (120ml) was added dropwise an ice cooled solution of **2.14** *N*-[(benzyloxy)carbonyl]-*D*-methionine methyl ester (28.96g, 0.102mol) in MeOH (300ml). The reaction mixture was stirred for 3 hours. The precipitate was filtered off using a Buchner funnel and washed with MeOH (3x100ml), the filtrates were combined and concentrated under reduced pressure to ca. 120ml. The concentrated solution was washed with CHCl₃ (3x150ml). The combined extracts were washed with water (200ml), dried with MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (CH₂Cl₂:MeOH, 95:5) gave **2.15** methyl *D*-2-[[[(benzyloxy)carbonyl]amino]-4-(methylsulfinyl) butanoate (28.14g, 92%) as a translucent white oil.

¹H NMR (300 MHz, CDCl₃) δ: 7.34 (m, 5H, Ar-H), 5.91 (s, 1H, NH), 5.03 (s, 2H, H-6), 4.34 (m, 1H, H-4), 3.67 (s, 3H, H-5), 2.90 (m, 2H, H-2), 2.51 (s, 3H, H-1) 2.30 (m, 2H, H-3).

Physical properties and spectra comparable to that reported in the literature.⁴⁸

2.16: *N*-[(benzyloxy)carbonyl]-*D*-vinylglycine methyl ester.

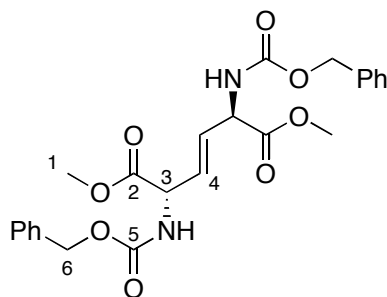


2.15 Methyl *D*-2-{[(benzyloxy)carbonyl]amino}-4-(methylsulfinyl) butanoate (3.52g, 11.8mmol) was Kugelrohr distilled at 150°C at 3mmHg. The pungent garlic smelling distillate was purified by column chromatography (EtOAc:PE, 15:85) as a light yellow oil followed by a second purification by column chromatography (EtOAc:PE, 1:9) to afford **2.16** *N*-[(benzyloxy)carbonyl]-*D*-vinylglycine methyl ester (1.57g, 56%) as a light yellow oil.

¹H NMR (500 MHz, CDCl₃) δ: 7.30 (m, 5H, Ar-H), 5.90 (m, 1H, H-2), 5.66 (s, 1H, NH), 5.36 (d, J=17Hz, 1H, H-1*E*), 5.26 (d, J=10.4Hz, 1H, H-1*Z*), 5.11 (s, 2H, H-5), 4.95 (s, 1H, H-3), 3.74 (s, 3H, H-4).

Physical properties and spectra comparable to that reported in the literature.⁴⁸

2.25: Dimethyl (2S,3E,5S)-2,5-bis{[(benzyloxy)carbonyl]amino}-3-hexenedioate.



To a stirring solution **2.16** (2*R*)-2-{[(benzyloxy)carbonyl]amino}-3-butenioate (0.608g, 2.45mmol) under a nitrogen atmosphere was added Grubbs 2nd generation catalyst (0.207g, 0.245mmol). The solution was refluxed for 18 hours. The solution was allowed to cool and the solvent was removed under reduced pressure. The dark brown oil was dissolved in a minimal amount of toluene (*ca.* 10ml) and loaded onto a pre-loaded column and the column was eluted with (EtOAc:PE, 1:4) to afford **2.25** dimethyl (2*S*,3*E*,5*S*)-2,5-bis{[(benzyloxy)carbonyl]amino}-3-hexenedioate. as a light yellow oil (0.238g, 74%).

m/z (ESI): 470, 462, 390, 334, 274.

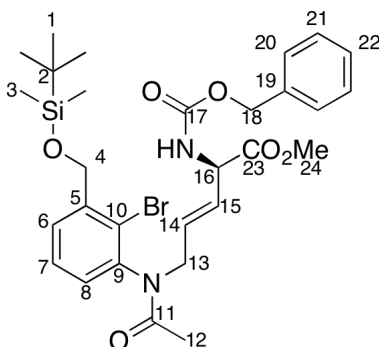
HRMS (ESI): Calcd. for C₂₄H₂₆N₂O₈ [M+Na]⁺: 493.1587 found: 493.1589

¹H NMR (500 MHz, CDCl₃) δ: 7.45 -7.22(m, 5H, Ar-H), 5.60 (s, 1H, N-H), 5.41 (s, H-4), 5.19 (s, 2H, H-5), 4.95 (s, 1H, H-3), 3.74 (s, 3H, H-1).

¹³C NMR (126 MHz, CDCl₃) δ: 170.43, 155.35, 136.04, 129.44, 129.06, 128.53, 128.24, 128.12, 67.24, 54.91, 52.88, 30.75.

*ν*_{max} (film/cm⁻¹): 3328.95 w, 2953.52 w, 1722.26 s, 1698.97 s, 1641.17 m., 1524.73 s.

2.26: Methyl (2*S*,3*E*)-5-[acetyl-2-bromo-3-({*tert*-butyl(dimethyl)silyl}oxy)methyl]anilino]-2-{{(benzyloxy)carbonyl}amino}-3-pentenoate



To a stirring solution of **2.10** 2-bromo-3-(*tert*-butyldimethylsilyloxymethyl)-*N*-acetyl-*N*-allylaniline (0.323g, 0.813mmol) and **2.16** (2*R*)-2-{{(benzyloxy)carbonyl}amino}-3-buten-1-ol (0.405g, 1.63mmol) under a nitrogen atmosphere was added Grubbs 2nd generation catalyst (0.138g, 0.163mmol). The solution was refluxed for 18 hours. The solution was allowed to cool and the solvent was removed under reduced pressure. The dark brown oil was dissolved in a minimal amount of toluene (*ca.* 10ml) and loaded onto a pre-loaded column. The column was eluted with (PE 100%, *ca.* 500ml), (PE:Et₂O, 1:1 *ca.* 500ml) and then (PE:Et₂O, 3:7 *ca.* 500ml) until all the product was isolated. The starting materials **2.10** 2-bromo-3-(*tert*-butyldimethylsilyloxymethyl)-*N*-acetyl-*N*-allylaniline (99mg, 31%) then by **2.16** (2*R*)-2-{{(benzyloxy)carbonyl}amino}-3-buten-1-ol (0.202g, 50%) were isolated first followed by the desired product **2.26** methyl (2*R*,3*E*)-5-[acetyl-2-bromo-3-({*tert*-butyl(dimethyl)silyl}oxy)methyl]anilino]-2-{{(benzyloxy)carbonyl}amino}-3-pentenoate as a light brown oil (0.332g, 66%) and finally **2.25** dimer (56.7mg, 15%).

$[\alpha]_D = -154.7^\circ$ (c 0.19, MeOH)

m/z (ESI): 620, 561, 469, 397, 299, 262, 220, 174, 149, 133, 117.

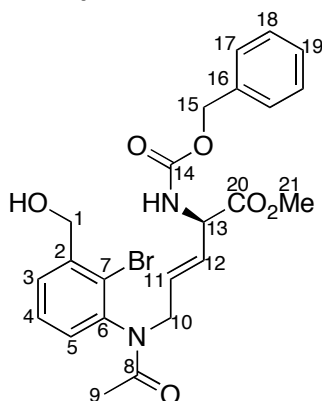
HRMS (ESI): Calcd. for C₂₉H₃₉BrN₂O₆ [M+Na]⁺: 641.1658 found: 641.1665

¹H NMR (500 MHz, CDCl₃) δ : 7.58 (t, *J* = 7.8, 1H, H-7), 7.36 (m, 6H, H-8, H-20, H-21, H-22), 7.00 (d, *J* = 7.7, 1H, H-6), 5.85 (m, 1H, H-14), 5.48 (dd, *J* = 15.2, 6.5, 1H, H-15), 5.40 (s, 1H, NH), 5.12 (s, 2H, H-18), 4.85 (s, 1H, H-16), 4.75 (s, 2H, H-4), 3.71 (s, 3H, H-24), 3.65 (dd, *J* = 14.3, 7.6, 2H, H-13), 1.77 (s, 3H, H-12), 0.98 (s, 9H, H-1), 0.16 (s, 6H, H-3).

¹³C NMR (126 MHz, CDCl₃) δ : 163.38, 166.35, 142.74, 140.81, 142.39, 137.09, 131.30, 129.02, 128.91, 128.76, 128.52, 127.84, 128.19, 128.04, 127.99, 127.72, 127.58, 126.81, 125.78, 122.02, 65.06, 25.92, 18.37, -5.11.

ν_{\max} (film/cm⁻¹): 3265.34 b, 1663.86 s, 1627.58 s, 1593.25 s, 1532.95 s, 1466.92 s

**2.28: Methyl (2S,3E)-5-[acetyl-2-bromo-3-(hydroxymethyl)anilino]-2-
{[(benzyloxy)carbonyl]amino}-3-pentenoate.**



Hydrofluoric acid (40%, 40 drops) was added dropwise to a stirring solution of **2.26** methyl (2*R*,3*E*)-5-[acetyl-2-bromo-3-({*tert*-butyl(dimethyl)silyl}oxy)methyl)anilino]-2-{{[(benzyloxy)carbonyl]amino}-3-pentenoate (1.24g, 3.11mmol) in MeCN (40ml) and the solution was stirred at room temperature for an hour. A saturated solution of sodium bicarbonate (25ml) was added, the organic layer was separated and the aqueous phase was extracted with EtOAc (3x20ml). The organic extracts were combined, dried with magnesium sulphate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography to give **2.28** methyl (2*S*,3*E*)-5-[acetyl-2-bromo-3-(hydroxymethyl)anilino]-2-{{[(benzyloxy)carbonyl]amino}-3-pentenoate (0.858g, 97%) as a colourless oil.

$[\alpha]_D = -165.1^\circ$ (c 0.26, MeOH)

m/z (ESI): 541, 529, 248, 222, 175, 99.

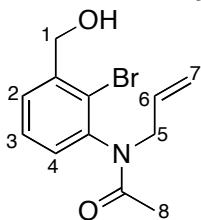
HRMS (ESI): Calcd. for $C_{23}H_{25}BrN_2O_6$ $[M+Na]^+$: 527.0781 found: 527.0788

1H NMR (500 MHz, $CDCl_3$) δ : 7.62 (t, $J = 7.8$, 1H, H-4), 7.39 (m, 6H, H-5, H-17, H-18, H-19), 7.08 (d, $J = 7.7$, 1H, H-3), 5.79 (m, 1H, H-11), 5.51 (dd, $J = 15.2, 6.5$, 1H, H-12), 5.38 (s, 1H, NH), 5.12 (s, 2H, H-15), 4.85 (s, 1H, H-13), 4.45 (s, 2H, H-1), 3.82 (s, 1H, OH), 3.73 (s, 3H, H-21), 3.67 (dd, $J = 14.3, 7.6$, 2H, H-13), 1.77 (s, 3H, H-19).

^{13}C NMR (126 MHz, $CDCl_3$) δ : 166.68, 164.51, 154.09, 143.46, 136.62, 135.57, 135.34, 128.47, 128.22, 127.94, 126.35, 124.02, 123.49, 121.27, 77.26, 77.00, 76.75, 67.87, 52.83, 51.85, 38.17.

ν_{max} (film/ cm^{-1}): 3282 b, 1667 s, 1627 s, 1593 s, 1532 s, 1466 s

2.30: 3-(*N*-Acety-*N*-allylamino)-2-bromobenzyl alcohol.

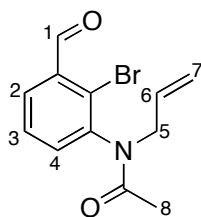


Hydrofluoric acid (40%, 40 drops) was added dropwise to a stirring solution of **2.10** 2-bromo-3-(*tert*-butyldimethylsilyloxymethyl)-*N*-acetyl-*N*-allylaniline (1.24g, 3.11mmol) in MeCN (40ml) and the solution was stirred at room temperature for an hour. A saturated solution of sodium bicarbonate (25ml) was added, the organic layer was separated and the aqueous phase was extracted with EtOAc (3x20ml). The organic extracts were combined, dried with magnesium sulphate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography to give **2.30** 3-(*N*-Acety-*N*-allylamino)-2-bromobenzyl alcohol (0.858g, 97%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ: 7.58 (d, J=7.8Hz, 1H, H-4), 7.34 (t, J=7.7Hz, 1H, H-3), 7.09 (d, J=7.7Hz, 1H, H-2), 5.83 (m, H-6), 5.05 (d, J=10.1Hz, 1H, H-7Z), 5.00 (d, J=17.8 Hz), 4.75 (s, 2H, H-1), 3.79 (s, 1H, OH), 3.61 (m, 2H, H-5), 1.74 (s, 1H, H-8).

Physical properties and spectra comparable to that reported in the literature.^{25, 26, 27}

2.31: 3-(*N*-Acety-*N*-allylamino)-2-bromobenzaldehyde.

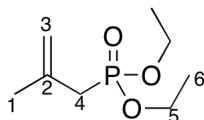


Activated manganese(IV) oxide (3.0g, 25mmol) was added to a stirring solution of **2.30** 3-(*N*-Acety-*N*-allylamino)-2-bromobenzyl alcohol (0.714g, 2.51mmol) in anhydrous THF and the mixture was stirred overnight. The mixture was filtered through a plug of Celite®, the residue was washed with EtOAc (ca. 40ml). The filtrate and the washings were combined and the solvent was removed under reduced pressure to give **2.31** 3-(*N*-acety-*N*-allylamino)-2-bromobenzaldehyde (0.581g, 82%) as a cream solid.

¹H NMR (500 MHz, CDCl₃) δ: 10.40 (s, 1H, H-1), 7.92 (d, 7.5Hz, 1H, H-4), 7.49 (t, J=7.6Hz, 1H, H-3), 7.45 (d, J=7.7Hz, 1H, H-2), 5.87 (m, 1H, H-6), 5.11 (d, J=11Hz, H-7Z), 5.03 (d, J=17.1Hz, 1H, H-7E), 3.69 (m, 1H, H-5), 1.81 (s, 3H, H-8).

Physical properties and spectra comparable to that reported in the literature.^{25, 26, 27}

2.33: Diethyl 2-methyl-2-propenylphosphonate.

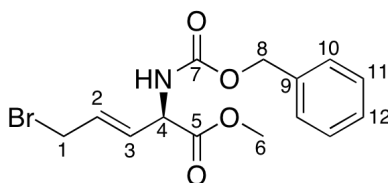


To a stirring suspension of methylallyl chloride (15.87g, 175mmol) and KI (29.09g, 175mmol) in acetone:CH₃CN 5:4 (875ml) was added triethyl phosphite (31.92g, 175mmol). The mixture was stirred for 12hr at room temperature and then heated to 60°C and stirred for a further 5hr. Filtration of the mixture through a Buchner funnel followed by washing of the residue with acetone (3x100ml). The filtrates were combined and the solvent was removed under reduced pressure to give a residue that was purified by Kugelhour distillation (77°C, 3mmHg) to give **2.33** diethyl 2-methyl-2-propenylphosphonate (29.30g, 87%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ: 4.84 (dd, J = 3.1, 1.5, 1H, H-3), 4.79 (d, J = 4.7, 1H, H-3), 4.06 – 3.97 (m, 4H, H-5), 2.49 (d, J = 22.3, 2H, H-4), 1.79 (s, 3H, 1.79), 1.23 (t, J = 7.1, 6H, H-6).

Physical properties and spectra comparable to that reported in the literature.⁷⁰

2.36: Methyl (2*R*,3*E*)-2-[[[(benzyloxy)carbonyl]amino]-5-bromo-3-pentenoate.



To a solution of **2.16** methyl (2*R*)-2-[[[(benzyloxy)carbonyl]amino]-3-butenate (0.296g, 1.19mmol) and allyl bromide (1.44g, 11.9mmol) in CH₂Cl₂ (15ml) under a nitrogen atmosphere was added Grubbs 2nd generation catalyst (0.100g, 0.119mmol). The solution was refluxed for 18 hours. The solution was allowed to cool and the solvent was removed under reduced pressure. The dark brown oil was dissolved in a minimal amount of toluene (*ca.* 5ml) and loaded onto a pre-loaded column. The column was eluted with (PE 100%, *ca.* 500ml) and then (PE:EA, 17:3) to give **2.36** Methyl (2*R*,3*E*)-2-[[[(benzyloxy)carbonyl]amino]-5-bromo-3-pentenoate as an orange oil (0.346g, 85%). *R*_f=0.25 (EA:PE, 1:4).

[α]_D = -124.6° (*c* 0.67, MeOH)

m/z (EI⁺): 282, 262, 238, 190, 157, 108, 92.

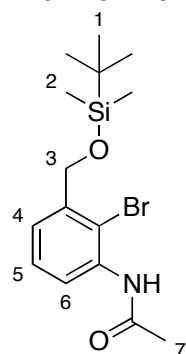
HRMS (ESI): Calcd. for C₁₄H₁₆BrNO₄ [M+Na]⁺: 366.0140; found: 366.0127

¹H NMR (500 MHz, CDCl₃) δ : 7.39 – 7.31 (m, 5H, H-10, H-11, H-12), 5.98 (dt, *J* = 14.8, 7.3, 1H, H-2), 5.83 (dd, *J* = 15.0, 4.5, 1H, H-3), 5.49 (d, *J* = 4.5, 1H, H-4), 5.13 (s, 2H, H-8), 4.97 (s, 1H, NH), 3.93 (d, *J* = 7.1, 2H, H-1), 3.78 (s, 3H, H-6).

¹³C NMR (126 MHz, CDCl₃) δ : 170.43, 155.35, 136.04, 129.44, 129.06, 128.53, 128.24, 128.12, 67.24, 54.91, 52.88, 30.75.

ν_{max} (film/cm⁻¹): 3328 w, 2953 w, 1705 s, 1513 s, 1435 m.

2.38: 2-Bromo-3-(*tert*-butyldimethylsilyloxymethyl)-*N*-acetylaniline.

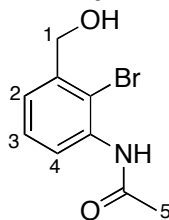


To a stirring solution of **2.08** 2-bromo-3-(*tert*-butyldimethylsilyloxymethyl)aniline (4.31g, 13.6mmol) in THF (130ml) was added freshly distilled acetyl chloride (1.94ml, 27.3mmol) was added and the solution was stirred at room temperature for an hour. The solution was quenched with saturated sodium bicarbonate solution (70ml), the organic layer was separated and the aqueous extract was washed with ethyl acetate (3x80ml). The organic layers were combined, dried with magnesium sulphate and the solvent was removed under reduced pressure. The crude extract was purified by column chromatography (PE:Et₂O, 3:2) to give **2.38** 2-bromo-3-(*tert*-butyldimethylsilyloxymethyl)-*N*-acetylaniline (4.44g, 91%) as a light yellow oil.

¹H NMR (500 MHz, CDCl₃) δ: 8.22 (s, 1H, H-6), 7.76 (s, 1H, NH), 7.34 (d, J = 7.7, 1H, H-4), 7.30 (t, J = 7.9, 1H, H-5), 4.75 (s, 2H, H-3), 2.23 (s, 3H, H-7), 0.97 (s, 9H, H-1), 0.04 (s, 6H, H-2).

Physical properties and spectra comparable to that reported in the literature.^{25, 26, 27}

2.39: 3-(*N*-Acetylamino)-2-bromobenzyl alcohol.

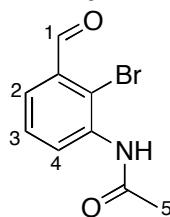


Hydrofluoric acid (40%, 80 drops) was added dropwise to a stirring solution of **2.38** 2-bromo-3-(*tert*-butyldimethylsilyloxymethyl)-*N*-acetylaniline (4.02g, 11.2mmol) in MeCN (100ml) and the solution was stirred at room temperature for an hour. A saturated solution of sodium bicarbonate (75ml) was added, the organic layer was separated and the aqueous phase was extracted with EtOAc (3x60ml). The organic extracts were combined, dried with magnesium sulphate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography to give **2.39** 3-(*N*-acetylamino)-2-bromobenzyl alcohol (2.60g, 95%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ: 8.21 (s, 1H, H-4), 7.74 (s, 1H, NH), 7.32 (d, J = 7.5, 1H, H-2), 7.27 (t, J = 7.9, 1H, H-3), 4.65 (s, 2H, H-1), 3.76 (s, 1H, OH), 2.20 (s, 3H, H-5).

Physical properties and spectra comparable to that reported in the literature.^{25, 26, 27}

2.40: 3-(*N*-Acetylamino)-2-bromobenzaldehyde.

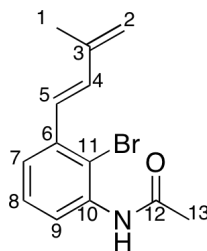


Activated manganese(IV) oxide (10.96g, 92.1mmol) was added to a stirring solution of **2.39** 3-(*N*-acetylamino)-2-bromobenzyl alcohol (2.25g, 9.21mmol) in anhydrous THF (100ml) and the mixture was stirred overnight. The mixture was filtered through a plug of Celite®, the residue was washed with EtOAc (ca. 100ml). The filtrate and the washings were combined and the solvent was removed under reduced pressure to give **2.40** 3-(*N*-Acetylamino)-2-bromobenzaldehyde (1.96g, 88%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ: 10.35 (s, 1H, H-1), 8.17 (s, 1H, H-4), 7.72 (s, 1H, NH), 7.34 (d, J = 7.6, 1H, H-2), 7.27 (t, J = 7.8, 1H, H-3), 2.23 (s, 3H, H-5).

Physical properties and spectra comparable to that reported in the literature.^{25, 26, 27}

2.41: *N*-{2-bromo-3-[(*E*)-3-methyl-1,3-butadienyl]phenyl}acetamide.



To a solution of dimethyl 2-methyl-2-propenylphosphonate (0.600g, 3.12mmol) in anhydrous THF (15ml) was added ⁿBuLi (1.6M in hexanes, 1.95ml, 3.12mmol) at -78°C. After stirring for 15 minutes a solution of *N*-(2-bromo-3-formylphenyl)acetamide (0.378g, 1.56mmol) was added in HMPA (1.05ml, 6mmol) was added dropwise via canular. The resulting yellow solution was stirred for 2 hours at -78°C. The solution was allowed to warm to room temperature and was stirred overnight. The solution was quenched with saturated aqueous NH₄Cl solution. The organic layer was isolated and the aqueous was washed with Et₂O (3x15ml). The combined organic fractions were washed with brine (30ml), dried with MgSO₄ and concentrated to afford a yellow oil. Purification by flash chromatography (PE:Et₂O, 3:1) yielded a white solid (0.346g, 79%). R_f = 0.34 (PE:Et₂O, 3:1).

m. p. = 124.9 to 125.5 °C

m/z (ESI): 304, 302, 222, 166, 100.

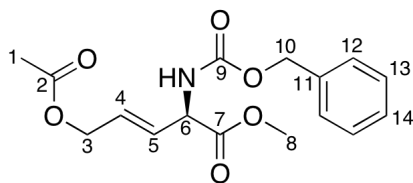
HRMS (ESI): Calcd. for C₁₃H₁₄NOBr [M+Na]⁺: 302.0150; found: 302.0143

¹H NMR (500 MHz, CDCl₃) δ 8.19 (s, 1H, H-9), 7.74 (s, 1H, NH), 7.32 (d, J = 7.4, 1H, H-7), 7.27 (t, J = 7.9, 1H, H-8), 6.85 (d, J = 15.9, 1H, H-5), 6.77 (d, J = 15.9, 1H, H-4), 5.17 (s, 1H, H-2), 5.15 (s, 1H, H-2), 2.24 (s, 3H, H-13), 2.01 (s, 3H, H-1).

¹³C NMR (126 MHz, CDCl₃) δ: 141.87, 136.01, 135.05, 127.77, 127.66, 122.29, 120.76, 118.74, 109.98, 29.67, 24.89, 18.52.

ν_{max} (film/cm⁻¹): 3270 m, 2920 m, 1723 w, 1660 s, 1601 m, 1585 m, 1532 s.

2.59: Methyl (2*R*,3*E*)-5-(acetyloxy)-2-[[[(benzyloxy)carbonyl]amino]-3-pentenoate



To a solution of methyl (2*R*)-2-[[[(benzyloxy)carbonyl]amino]-3-butenate (1.24g, 4.97mmol) and allyl acetate (4.98g, 49.7mmol) in CH₂Cl₂ (40ml) under a nitrogen atmosphere was added Grubbs 2nd generation catalyst (0.422g, 0.497mmol). The solution was refluxed for 18 hours. The solution was allowed to cool and the solvent was removed under reduced pressure. The dark brown oil was dissolved in a minimal amount of toluene (*ca.* 5ml) and loaded onto a pre-loaded column. The column was eluted with (PE 100%, *ca.* 500ml and then (PE:EA, 17:3) yielding methyl (2*R*,3*E*)-5-(acetyloxy)-2-[[[(benzyloxy)carbonyl]amino]-3-pentenoate as an oil (0.57g, 36%). *R*_f = 0.33 (PE:EA, 17:3).

[α]_D = -137.2° (c 0.72, MeOH)

m/z (ESI): 344, 300, 213, 114, 99.

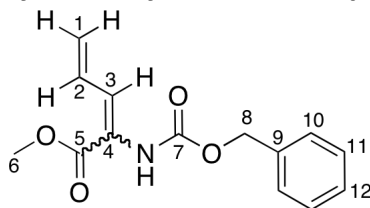
HRMS (ESI): Calcd. for C₁₆H₁₉NO₆ [M+Na]⁺: 344.1105; found: 344.1105.

¹H NMR (500 MHz, CDCl₃) δ : 7.39 – 7.29 (m, 5H, H-12, H-13, H-14), 5.91 – 5.78 (m, 2H, H-4, H-5), 5.54 (s, 1H, NH), 5.12 (s, 2H, H-10), 4.96 (s, 1H, H-6), 4.56 (d, J = 4.8, 2H, H-3), 3.76 (s, 3H, H-8), 2.05 (s, 3H, H-1).

¹³C NMR (126 MHz, CDCl₃) δ : 170.65, 170.49, 136.09, 128.51, 128.29, 128.20, 128.15, 128.10, 128.02, 127.60, 67.16, 63.52, 55.17, 52.79, 20.80.

ν_{max} (film/cm⁻¹): 2922.20 w, 1715.29 s, 1515.90 m, 1455.46 m.

2.66: Methyl 2-{[(benzyloxy)carbonyl]amino}-2,4-pentadienoate



To solution of $\text{Pd}_2(\text{dba})_3$ (28.1mg, 0.0307mmol) and dppb (26.1mg, 0.0613mmol) in THF (10ml) under a nitrogen atmosphere was added *via* cannula a solution of (2*R*,3*E*)-5-(acetyloxy)-2-{[(benzyloxy)carbonyl]amino}-3-pentenoate (0.197g, 0.613mmol) in THF (1ml), the solution was allowed to stir for ten minutes. A solution of *N*-{2-bromo-3-[(1*E*)-3-methyl-1,3-butadienyl]phenyl}acetamide (0.206g, 0.736mmol) in THF (1ml) was added *via* cannula. The solution was heated to reflux for 3 hours until complete consumption of (2*R*,3*E*)-5-(acetyloxy)-2-{[(benzyloxy)carbonyl]amino}-3-pentenoate by TLC. The solution was allowed to cool and filtered through Celite®. The Celite® was washed with Et_2O (3x20ml). The solvent was removed under reduced pressure. The crude extract was purified by column chromatography to give 2-{[(benzyloxy)carbonyl]amino}-2,4-pentadienoate as an oil (0.125g, 78%). $R_f = 0.35$ (EA:PE, 1:4).

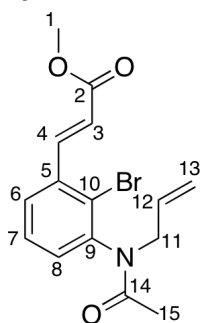
HRMS (ESI): Calcd. for $\text{C}_{14}\text{H}_{16}\text{BrNO}_4$ $[\text{M}+\text{Na}]^+$: 284.0893; found: 284.0889

^1H NMR (500 MHz, CDCl_3) δ : 7.37 (s, 5H, H-10, H-11, H-12), 7.00 (d, $J = 11.2$, 1H, H-3), 6.59 (dt, $J = 17.0, 10.7$, 1H, H-2), 6.41 (s, 1H, NH), 5.60 (d, $J = 16.9$, 1H, H-1*E*), 5.48 (d, $J = 10.0$, 1H, H-1*Z*), 5.16 (s, 2H, H-8), 3.78 (s, 3H, H-6).

^{13}C NMR (126 MHz, CDCl_3) δ : 165.25, 135.85, 131.46, 128.53, 128.30, 128.24, 124.94, 110.20, 67.56, 52.54.

ν_{max} (film/ cm^{-1}): 3328 w, 2953 w, 1722 s, 1698 s, 1641 m., 1524 s.

2.67: Methyl (2E)-3-{3-[acetyl(allyl)amino]-2-bromophenyl}-2-propenoate



N-allyl-*N*-(2-bromo-3-formylphenyl)acetamide (2.165g, 7.62mmol) was dissolved in CH₂Cl₂ (30ml) under a nitrogen atmosphere. 2-methoxy-3-(triphenylphosphoranylidene)propanal (3.05g, 9.14mmol) was added in portions. The solution was allowed to stir for 3hr at room temperature. The solvent was removed under reduced pressure. The white-grey solid was dissolved in a minimal amount of toluene and was loaded onto a pre-loaded column. The column was eluted with (PE:Et₂O, 3:7) to give methyl (2*E*)-3-{3-[acetyl(allyl)amino]-2-bromophenyl}-2-propenoate as a yellow solid (2.30g, 89%). *R*_f = 0.28 (PE:Et₂O, 3:7).

m. p. 84.9 to 86.7 °C

m/z (ESI): 360, 120, 101, 58

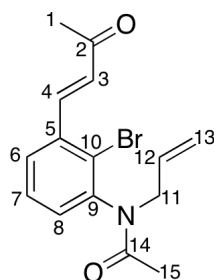
HRMS (ESI): Calcd. for C₁₅H₁₆BrNO₃ [M+Na]⁺: 360.0206; found: 360.0205

¹H NMR (500 MHz, CDCl₃) δ 8.07 (d, *J* = 15.9, 1H, H-4), 7.59 (dd, *J* = 7.9, 1.3, 1H, H-8), 7.37 (t, *J* = 7.8, 1H, H-7), 7.22 (dd, *J* = 7.7, 1.3, 1H, H-6), 6.40 (d, *J* = 15.9, 1H, H-3), 5.92 – 5.83 (m, 1H, H-12), 5.10 (d, *J* = 10.1, 1H, H-13*Z*), 5.05 (d, *J* = 17.1, 1H, H-13*E*), 3.83 (s, 3H), 3.68 – 3.62 (m, 2H, H-11), 1.80 (s, 3H, H-15).

¹³C NMR (126 MHz, CDCl₃) δ 169.79, 166.39, 142.84, 142.43, 137.11, 132.61, 132.03, 130.33, 128.29, 127.46, 121.97, 118.69, 51.94, 50.81, 22.39.

*ν*_{max} (film/cm⁻¹): 2946 m, 1718 s, 1655 s, 1567 m, 1467 m, 1431 m, 1384 s.

2.68 *N*-allyl-*N*-{2-bromo-3-[(1*E*)-3-oxo-1-butenyl]phenyl}acetamide



To a stirring solution of *N*-allyl-*N*-(2-bromo-3-formylphenyl)acetamide (3.77g, 13.4mmol) in CH_2Cl_2 (40ml) under nitrogen was added 1-(triphenylphosphoranylidene)acetone (5.07g, 16.0mmol) in portions. Once the entire solid had dissolved the solution was stirred for 3 hours. The solvent was removed under reduced pressure. The grey solid was dissolved in a minimal amount of toluene (*ca.* 10ml) and loaded onto a pre-packed column. The column was eluted with Et_2O :PE, 8:2 isolating *N*-allyl-*N*-{2-bromo-3-[(1*E*)-3-oxo-1-butenyl]phenyl}acetamide (3.96g, 92%) as a yellow solid. R_f = 0.32 (Et_2O :PE, 8:2).

m. p. = 58.9 to 60.0 °C

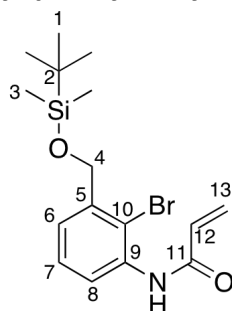
m/z (EI): 322, 288, 242, 200, 159, 43.

^1H NMR (500 MHz, C_6D_6) δ : 7.81 (d, J = 16.3, 1H, H-4), 7.52 (dd, J = 1.3, 7.8, 1H, H-8), 7.30 (t, J = 7.7, 1H, H-7), 7.14 (dd, J = 1.4, 7.7, 1H, H-6), 6.54 (d, J = 16.3, 1H, H-3), 5.78 (dddd, J = 5.6, 7.7, 10.1, 15.8, 1H, H-12), 5.01 (d, J = 9.4, 1H, H-13*E*), 4.95 (d, J = 18.3, 1H, H13*Z*), 3.57 (dd, J = 7.8, 14.6, 1H), 2.33 (s, 3H, H-1), 1.72 (s, 3H, H-15).

^{13}C NMR (126 MHz, C_6D_6) δ 206.69, 197.73, 169.97, 169.70, 142.37, 141.34, 137.03, 132.68, 132.46, 132.10, 130.77, 129.60, 128.31, 128.11, 128.00, 127.42, 127.00, 118.67, 118.32, 64.83, 50.77, 50.70, 30.76, 30.21, 27.21, 22.30, 22.27.

ν_{max} (film/ cm^{-1}): 2926 w, 2668 s, 1647 s, 1568 m, 1467 m, 1414 s, 1390 s

2.77: *N*-[2-bromo-3-({*tert*-butyl(dimethyl)silyl}oxy)methyl]phenyl]acrylamide



Acryloyl chloride was freshly prepared from acrylic acid.⁵⁸ 2-bromo-3-({*tert*-butyl(dimethyl)silyl}oxy)methyl]aniline (5.285g, 16.8mmol) was dissolved in CH₂Cl₂ (50ml), NEt₃ (4.72ml, 33.6mmol) was added and the solution was cooled to 0°C. Acryloyl chloride was added to the stirring solution dropwise over 15 minutes, maintaining the temperature at 0°C. The solution was allowed to warm to room temperature and was stirred for 2 hours. The reaction was quenched with saturated aqueous sodium hydrogen carbonate. The organic layer was separated and the remaining aqueous extract was washed with CH₂Cl₂ (2x30ml) and Et₂O (2x30ml). The organic fractions were combined and the solvent was removed under reduced pressure to give the crude product. Purification by column chromatography with (Et₂O:PE, 1:3) gave *N*-[2-bromo-3-({*tert*-butyl(dimethyl)silyl}oxy)methyl]phenyl]acrylamide as a yellow solid (4.95g, 80%). R_f = 0.27 (Et₂O:PE, 1:3).

m. p. = 67.3 to 68.5 °C

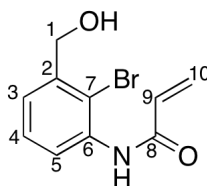
HRMS (ESI): Calcd. for C₁₆H₂₄BrNO₂Si [M+Na]⁺: 392.0657; found: 392.0663

¹H NMR (500 MHz, CDCl₃) δ: 8.30 (s, 1H, NH), 7.86 (s, 1H, H-8), 7.35 – 7.32 (m, 2H, H-6, H-7), 6.44 (d, J = 16.8, 1H, H-13_E), 6.31 (dd, J = 16.9, 10.2, 1H, H-12), 5.79 (d, J = 10.2, 1H, H-13_Z), 4.73 (s, 2H, H-4), 0.97 (s, 9H, H-1), 0.14 (s, 6H, H-3).

¹³C NMR (126 MHz, CDCl₃) δ: 163.38, 140.81, 135.09, 131.30, 127.89, 127.84, 123.34, 122.65, 121.76, 120.68, 65.06, 25.92, 18.37, -5.11,

ν_{max} (film/cm⁻¹): 3328 m, 2926 m, 2854 m, 1682 m, 1622 s, 1596 s, 1518 s, 1465 s.

2.78: *N*-[2-bromo-3-(hydroxymethyl)phenyl]acrylamide



N-[2-bromo-3-({*tert*-butyl(dimethyl)silyl}oxy)methyl]phenyl]acrylamide (2.42g, 6.53mmol) was dissolved in acrylonitrile (50ml). Hydrofluoric acid (*ca.* 20 drops) was added to the stirring solution at room temperature. The cloudy solution was stirred for 2 hours. Saturated aqueous sodium hydrogen carbonate (30ml) was added with care (effervescence!). The aqueous layer was separated and washed with EtOAc (3x20ml). The organic layers were combined and washed with saturated sodium chloride (30ml). The solvent was removed under reduced pressure. Purification by column chromatography (Et₂O:PE, 9:1), to give *N*-[2-bromo-3-(hydroxymethyl)phenyl]acrylamide as a white solid (1.58g, 94% yield). *R*_f = 0.22 (Et₂O:PE, 9:1).

m. p. = 136.3 to 137.2 °C.

m/z (ESI): 288, 224, 178, 100.

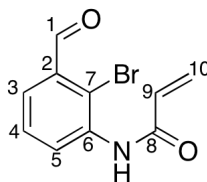
HRMS (ESI): Calcd. for C₁₀H₁₀BrNO₂ [M+Na]⁺: 277.9787 found: 277.9797

¹H NMR (500 MHz, CDCl₃) δ: 8.39 (d, *J* = 7.4, 1H, H-6), 7.83 (s, 1H, NH), 7.37 (t, *J* = 7.9, 1H, H-4), 7.29 (d, *J* = 7.4, 1H, H-3), 6.46 (d, *J* = 16.9, 1H, H-10*E*), 6.32 (dd, *J* = 16.9, 10.2, 1H, H-9), 5.84 (d, *J* = 10.2, 1H, H-10*Z*), 4.78 (d, *J* = 6.3, 2H, H-1), 1.55 (s, 1H, OH).

¹³C NMR (126 MHz, CDCl₃) δ 163.32, 140.79, 135.07, 131.29, 127.88, 123.29, 120.50, 77.24, 76.98, 76.73, 65.79, 65.05, 41.33, 34.09, 25.88, 22.57, 22.29, 20.40, 18.36, 15.22, 14.26, 13.99, -5.38.

*ν*_{max} (film/cm⁻¹): 3265 b, 1663 s, 1627 s, 1593 s, 1532 s, 1466 s

2.79: *N*-(2-bromo-3-formylphenyl)acrylamide



N-[2-bromo-3-(hydroxymethyl)phenyl]acrylamide (1.60g, 6.25mmol) was dissolved in THF (50ml). Manganese(IV)oxide (5.43g, 62.5mmol) was added to the stirring solution. The black mixture was stirred for 2hr at room temperature. The mixture was filtered through a cake of Celite®, the plug was washed with Et₂O (5x50ml). The yellow solution obtained was concentrated under reduced pressure to give a yellow oil. The crude product was purified by column chromatography (PE:Et₂O, 7:3) to give *N*-(2-bromo-3-formylphenyl)acrylamide as a white solid (1.33g, 84%). *R*_f = 0.33, (PE:Et₂O, 7:3).

m. p. = 129.1 to 130.3 °C.

m/z (ESI): 286, 222, 176, 98.

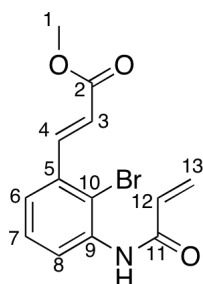
HRMS (ESI): Calcd. for C₁₀H₈BrNO₂ [M+Na]⁺: 275.9636 found: 275.9640

¹H NMR (500 MHz, CDCl₃) δ: 10.35 (s, 1H, H-1), 8.68 (d, *J* = 8.0, 1H, H-5), 7.93 (s, 1H, NH), 7.68 (dd, *J* = 7.6, 1.2, 1H, H-3), 7.46 (t, *J* = 7.9, 1H, H-4), 6.49 (d, *J* = 16.9, 1H, H-10*E*), 6.35 (dd, *J* = 16.9, 10.2, 1H, H-9), 5.87 (d, *J* = 10.2, 1H, H-10*Z*).

¹³C NMR (126 MHz, CDCl₃) δ: 191.14, 163.48, 136.43, 133.80, 130.87, 128.79, 128.38, 127.44, 125.80, 117.74, 109.99, 77.26, 77.01, 76.75.

*ν*_{max} (film/cm⁻¹): 3255 m, 3073w, 1687 s, 1661s, 1626 s, 1586 m, 1574 m, 1528 s.

2.80: Methyl (2E)-3-[3-(acryloylamino)-2-bromophenyl]-2-propenoate



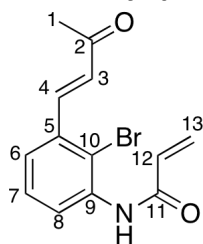
N-(2-bromo-3-formylphenyl)acrylamide (0.870g, 3.42mmol) was dissolved in CH₂Cl₂ under nitrogen. Methyl (triphenylphosphoranylidene)acetate (1.37g, 4.11mmol) was added in portions to the stirring solution. Once all the phosphoranylidene had dissolved the solution was stirred for 3 hours at room temperature. The reaction mixture was concentrated under reduced pressure, dissolved in a minimal amount of toluene and transferred directly onto a pre-loaded silica column. The column was eluted with (PE:Et₂O, 3:2) to give methyl (2E)-3-[3-(acryloylamino)-2-bromophenyl]-2-propenoate as a white solid (0.85g, 86%). R_f = 0.37 (PE:Et₂O, 3:2).

m. p. = 84.9 to 86.7 °C

HRMS (ESI): Calcd. for C₁₃H₁₂BrNO₃ [M+Na]⁺: 331.9892 found: 331.9907

¹H NMR (500 MHz, CDCl₃) δ: 8.49 (s, 1H, H-8), 8.05 (d, J = 15.8, 1H, H-4), 7.90 (s, 1H, NH), 7.36 (m, 2H, H-6, H-7), 6.46 (d, J = 16.9, 1H, H-13E), 6.39 (d, J = 15.8, 1H, H-3), 6.32 (dd, J = 16.9, 10.5, 1H, H-12), 6.30 (d, J = 10.5, 1H, H-13Z), 3.83 (s, 3H, H-1).

¹³C NMR (126 MHz, CDCl₃) δ: 163.82, 141.58, 140.79, 136.84, 135.73, 131.65, 128.68, 128.54, 122.11, 121.97, 120.09, 52.10

2.81: *N*-{2-bromo-3-[(1*E*)-3-oxo-1-butenyl]phenyl}acrylamide

N-(2-bromo-3-formylphenyl)acrylamide (0.32g, 1.26mmol) was dissolved in CH₂Cl₂ (20ml) under a nitrogen atmosphere. 1-(triphenylphosphoranylidene)acetone (0.481g, 1.51mmol) was added in portions to the stirring solution. Once all the phosphoranylidene had dissolved the solution was stirred for 3 hours at room temperature. The reaction mixture was concentrated under reduced pressure, dissolved in a minimal amount of toluene and transferred directly onto a pre-loaded silica column. The column was eluted with (PE:Et₂O, 1:1) to give *N*-{2-bromo-3-[(1*E*)-3-oxo-1-butenyl]phenyl}acrylamide as a white solid (0.303g, 82%). *R*_f = 0.32 (PE:Et₂O, 1:1).

m. p. = 167.1 to 168.3 °C.

m/z (ESI): 316, 310, 152, 100.

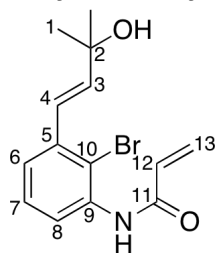
HRMS (ESI): Calcd. for C₁₃H₁₂BrNO₂ [M+Na]⁺: 315.9949 found: 315.9955.

¹H NMR (500 MHz, CDCl₃) δ: 8.50 (d, *J* = 6.4, 1H, H-8), 7.88 (d, *J* = 16.1, 1H, H-4), 7.88 (s, 1H, NH), 7.41 – 7.35 (m, 2H, H-6, H-7), 6.64 (d, *J* = 16.1, 1H, H-3), 6.47 (dd, *J* = 16.9, 0.7, 1H, H-13*E*), 6.33 (dd, *J* = 16.9, 10.3, 1H, H-12), 5.86 (dd, *J* = 10.3, 0.7, 1H, H-13*Z*), 2.42 (s, 3H, H-1).

¹³C NMR (126 MHz, CDCl₃) δ: 170.25, 141.88, 136.39, 135.21, 131.49, 130.35, 128.32, 128.15, 122.11, 121.97, 123.34, 27.88.

*ν*_{max} (film/cm⁻¹): 3255 m, 2922 s, 1683 s, 1662 s, 1609 s, 1536 s, 1468 s.

2.96: *N*-{2-bromo-3-[(1*E*)-3-hydroxy-3-methy-1-butenyl]phenyl}acrylamide.



N-{2-bromo-3-[(1*E*)-3-oxo-1-butenyl]phenyl}acrylamide (0.620g, 2.11mmol) was dissolved in THF (20ml) and the solution was cooled to -78°C . Methyl lithium (3.09ml, 4.63mmol) was added dropwise to the stirring solution maintaining the temperature below -75°C . Once addition was complete the solution was allowed to warm to room temperature. The solution was stirred for an hour at room temperature. Saturated aqueous ammonium chloride solution (15ml) was added to the solution and the organic layer was separated. The aqueous phase was washed with diethyl ether (3x20ml) and the organic layers were combined. The organic phase was washed with saturated brine solution (3x30ml). The solvent was removed under reduced pressure and the crude extract was purified by column chromatography (PE:Et₂O, 1:1) to afford tertiary alcohol (0.556g, 85%). $R_f = 0.36$ (PE:Et₂O, 1:1).

m/z (EI): 311, 296, 266, 230, 214, 188, 172, 160.

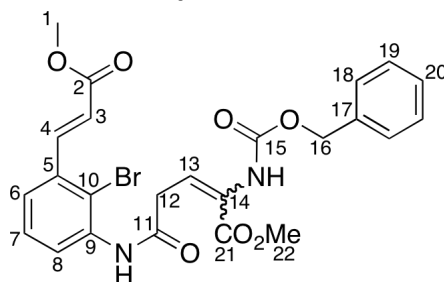
HRMS (ESI): Calcd. for C₁₃H₁₂BrNO₂ [M+Na]⁺: 315.9949 found: 315.9955.

¹H NMR (500 MHz, CDCl₃) δ : 8.29 (s, 1H, NH), 7.90 (s, 1H, H-8), 7.24 (s, 2H, H-7, H-8), 6.90 (d, $J = 15.9$, 1H, H-4), 6.44 (dd, $J = 0.9, 16.9$, 1H, H-13*E*), 6.31 (dd, $J = 16.9, 10.5$, 1H, H-12), 6.29 (d, $J = 10.5$, 1H, H-13*Z*), 5.81 (d, 1H, $J = 15.8$, 1H, H-3), 1.44 (s, 6H, H-1).

¹³C NMR (126 MHz, CDCl₃) δ : 163.42, 141.45, 140.22, 137.76, 135.73, 131.29, 128.04, 127.80, 126.59, 125.71, 122.84, 71.05, 28.91.

ν_{max} (film/cm⁻¹): 3240 br, 2964 m, 1662 s, 1629 s, 1589 s, 1530s.

2.98: Methyl 2-[[[(benzyloxy)carbonyl]amino}-5-{2-bromo-3-[(1E)-3-methoxy-3-oxo-1-propenyl]anilino}-5-oxo-2-pentenoate.



To a stirring solution of methyl (2E)-3-[3-(acryloylamino)-2-bromophenyl]-2-propenoate (0.336g, 1.08mmol) and methyl (2R)-2-[[[(benzyloxy)carbonyl]amino}-3-butenolate (0.270g, 1.08mmol) under a nitrogen atmosphere was added Grubbs 2nd generation catalyst (0.0919g, 0.0108mmol). The resulting brown solution was refluxed at 40°C for 18 hours. The solution was cooled and the solvent was removed under reduced pressure. The brown tar obtained was dissolved in a minimal amount of toluene and transferred directly onto a pre-packed silica column. The column was eluted with (PE, 100%), (PE:Et₂O, 1:1), (PE:Et₂O, 1:3), (Et₂O, 100%). A green oil was obtained which was titrated with pentane to give a white solid (0.372g, 63%). R_f = 0.23 (Et₂O).

m. p. = 169.2 to 171.1 °C

m/z (ESI): 553, 493, 413, 398, 330, 301, 279, 184, 100.

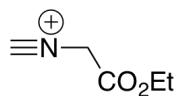
HRMS (ESI): Calcd. for C₂₄H₂₃BrN₂O₇ [M+Na]⁺: 553.0580 found: 553.0617.

¹H NMR (500 MHz, CDCl₃) δ: 8.49 (s, 1H, NHPh), 8.26 (d, J = 7.5, 1H, H-8), 8.05 (d, J = 15.8, 1H, H-4), 7.40 – 7.30 (m, 6H, H-6, H-7, H-18, H-19, H-20), 6.83 (t, J = 7.7, 1H, H-13), 6.77 (s, 1H, NHCO), 6.37 (d, J = 15.8, 1H, H-3), 5.18 (s, 2H, H-16), 3.83 (s, 3H, H-1), 3.81 (s, 3H, H-22), 3.42 (d, J = 7.6, 2H, H-12).

¹³C NMR (126 MHz, CDCl₃) δ: 166.68, 164.51, 154.09, 143.46, 136.62, 135.57, 135.34, 128.63, 128.47, 128.22, 127.94, 126.35, 124.02, 123.49, 121.27, 77.26, 77.00, 76.75, 67.87, 52.83, 51.85, 38.17.

*v*_{max} (film/cm⁻¹): 3264 m, 2920 m, 1723 s, 1691 s, 1651 s, 1510 .

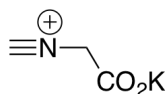
2.112: 2-Ethoxy-N-methyldiyn-2-oxoethanaminium



Formate **2.111** (5.0g, 0.0382mol) was dissolved in NEt₃ (26.5ml, 0.191mol) and THF (50ml) and was cooled to -78°C. An addition funnel was attached to the reaction and was charged with POCl₃ (4.26ml, 0.0458mol) in THF (28ml). The solution was added dropwise over a period of 30mins and then allowed to stir for a further 30mins. The resulting red-orange solution was warmed to 0°C and allowed to stir for an additional hour upon which ice water (50ml) was slowly added to the solution. The organic layer was separated and aqueous phase was washed with Et₂O (3x50ml). The organic extracts were combined, dried with MgSO₄ and concentrated under reduced pressure to give a foul smelling red oil which was distilled in vacuo (85°C, ca. 5mmHg) to give **2.112** (3.65g, 75%) as a light yellow oil.

Physical properties and spectra comparable to that reported in the literature.⁹⁸

2.113 Potassium carboxy-N-methyldynemethanaminium

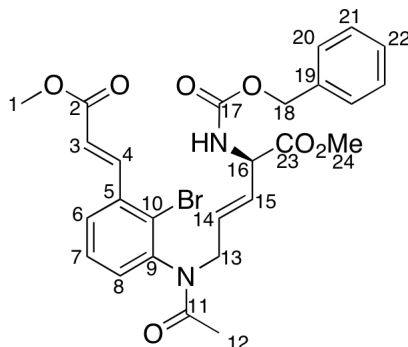


A solution of **2.112** (3.50g, 0.0306mol) and powdered KOH (1.72g, 0.0306mol) in THF (20ml) and distilled water (5ml) was stirred vigorously for 5 hours. The reaction was then concentrated and pumped on overnight to give an off white solid. The solid was collected with a Buchner funnel and subsequently washed with Et₂O to remove any unreacted isocyanide. The solid was then pulverised using a pestle and mortar and the resulting powder was transferred to a 100ml round bottom flask and stirred with Et₂O (50ml). The solid was then isolated on a Buchner funnel to give **2.113**, (2.96g, 78%) as an off-white solid.

Mp. 164 to 165 °C.

Physical properties and spectra comparable to that reported in the literature.⁹⁸

2.114: Methyl (2*R*,3*E*)-5-{acetyl-2-bromo-3-[(1*E*)-3-methoxy-3-oxo-1-propenyl]anilino}-2-[[[(benzyloxy)carbonyl]amino]-3-pentenoate



To a stirring solution of methyl (2*E*)-3-{3-[acetyl(allyl)amino]-2-bromophenyl}-2-propenoate (1.94g, 8.73mmol) and (2*R*)-2-[[[(benzyloxy)carbonyl]amino]-3-butenolate (1.42g, 8.73mmol) under a nitrogen atmosphere was added dichlorodicyanoquinone (0.101g, 0.873mmol) followed by Grubbs 2nd generation catalyst (0.486g, 0.873mmol). The dark blue solution was refluxed for 18 hours. The solution was allowed to cool and a methanolic solution of polar isocyanide **2.113** was added and the solution was allowed to stir for 30 minutes. The solvent was removed under reduced pressure to give a thick dark green-blue oil that was dissolved in a minimal amount of toluene (*ca.* 15ml) and loaded onto a pre-packed column. The column was eluted with 0.5L PE, 0.5L Et₂O:PE (1:3), 0.5L Et₂O:PE (1:1), 0.5L Et₂O:PE (3:1) and finally Et₂O until all the product was recovered. (2*R*)-2-[[[(benzyloxy)carbonyl]amino]-3-butenolate (0.706g) was recovered first, followed by methyl (2*E*)-3-{3-[acetyl(allyl)amino]-2-bromophenyl}-2-propenoate (0.712g), finally the desired product was isolated as a green oil. The product was subjected to a subsequent column isolating a white foam. *R*_f=0.34 (Et₂O).

$[\alpha]_D = -154.6^\circ$ (c 0.21, MeOH)

m/z (ESI): 583, 194, 100.

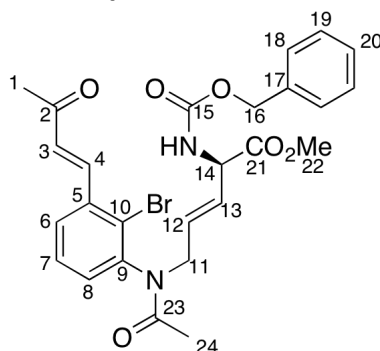
HRMS (ESI): Calcd. for C₂₆H₂₇BrN₂O₇ [M+Na⁺]: 581.089; found: 581.093.

¹H NMR (500 MHz, CDCl₃) δ 8.06 (d, *J* = 15.9, 1H, H-4), 7.57 (dd, *J* = 8.0, 14.7, 1H, H-8), 7.40 – 7.30 (m, 6H, H-7, H-20, H-21, H-22), 7.10 (d, *J* = 9.3, 1H, H-6), 6.40 (dd, *J* = 3.1, 15.9, 1H, H-3), 5.84 (m, 1H, H-14), 5.51 (dd, *J* = 5.7, 18.3, 1H, H-15), 5.43 (s, 1H, NH), 5.12 (s, 2H, H-18), 4.85 (m, 1H, H-16), 3.84 (s, 3H, H-1), 3.72 (s, 3H, H-24), 3.64 (m, 2H, H-13), 1.79 (s, 3H, H-12).

¹³C NMR (126 MHz, CDCl₃) δ 169.98, 166.35, 142.74, 142.46, 142.39, 137.09, 132.25, 130.30, 129.02, 128.91, 128.52, 128.39, 128.19, 128.04, 127.99, 127.72, 127.58, 126.81, 122.02, 67.01, 55.08, 52.68, 51.94, 51.46, 49.07, 29.64, 22.31.

ν_{\max} (film/cm⁻¹): 2952 w, 1714 s, 1659 s, 1522 m, 1434 m, 1390 m

2.115: Methyl (2*R*,3*E*)-5-{acetyl-2-bromo-3-[(1*E*)-3-oxo-1-butenyl]anilino}-2-[[[(benzyloxy)carbonyl]amino]-3-pentenoate



To a stirring solution of *N*-allyl-*N*-{2-bromo-3-[(1*E*)-3-oxo-1-butenyl]phenyl}acetamide (1.08g, 3.35mmol) and (2*R*)-2-[[[(benzyloxy)carbonyl]amino]-3-butenolate (1.25g, 5.03mmol) under a nitrogen atmosphere was added dichlorodicyanoquinone (88.9mg, 0.503mmol) followed by Grubbs 2nd generation catalyst (0.426g, 0.503mmol). The dark blue solution was heated to reflux for 18 hours. The solution was allowed to cool and a methanolic solution of polar isocyanide **2.113** was added and the solution was allowed to stir for 30 minutes. The solvent was removed under reduced pressure to give a thick dark green-blue oil that was dissolved in a minimal amount of toluene (*ca.* 15ml) and transferred onto a pre-packed column. The column was eluted with 0.5L PE, 0.5L Et₂O:PE (1:3), 0.5L Et₂O:PE (1:1), 0.5L Et₂O:PE (3:1) and finally Et₂O until all the product was recovered. (2*R*)-2-[[[(benzyloxy)carbonyl]amino]-3-butenolate (0.313g, 25%) was recovered first, followed by *N*-allyl-*N*-{2-bromo-3-[(1*E*)-3-oxo-1-butenyl]phenyl}acetamide (0.432g, 40%), then dimer (0.150g, 20%) finally the desired product methyl (2*R*,3*E*)-5-{acetyl-2-bromo-3-[(1*E*)-3-oxo-1-butenyl]anilino}-2-[[[(benzyloxy)carbonyl]amino]-3-pentenoate was isolated as a dark green oil. The product was subjected to a subsequent column isolating as a yellow oil (1.00g, 55%). *R*_f=0.28 (Et₂O).

$[\alpha]_D = -147.1^\circ$ (c 0.23, MeOH)

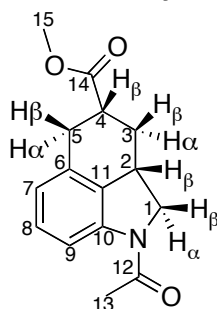
HRMS (ESI): Calcd. for C₂₆H₂₇BrN₂NaO₆ [M+Na]⁺: 565.0950; found: 565.0912

¹H NMR (500 MHz, CDCl₃) δ 7.89 (d, *J* = 16.3, 1H, H-4), 7.59 (dd, *J* = 7.8, 14.2, 1H, H-8), 7.40 – 7.29 (m, 6H, H-7, H-18, H-19, H-20), 7.12 (d, *J* = 7.4, 1H, H-6), 6.62 (dd, *J* = 3.7, 16.3, 1H, H-3), 5.94 – 5.77 (m, 1H, H-12), 5.51 (dd, *J* = 5.7, 18.3, 1H, H-13), 5.45 (m, 1H, H-14), 5.43 (s, 1H, NH), 5.12 (d, *J* = 2.6, 2H, H-16), 4.85 (m, 1H, H-14), 3.72 (s, 3H, H-22), 3.68 – 3.61 (m, 2H, H-11), 2.43 (s, 3H, H-1), 1.76 (s, 3H, H-24).

¹³C NMR (126 MHz, CDCl₃) δ 197.77, 169.74, 142.02, 141.98, 141.33, 137.14, 132.42, 130.89, 129.08, 128.97, 128.55, 128.53, 128.48, 128.42, 128.38, 128.24, 128.21, 128.05, 128.01, 127.67, 127.61, 127.57, 127.05, 127.01, 77.25, 76.99, 76.74, 67.09, 55.24, 55.06, 52.71, 48.95, 48.92, 29.66, 27.33, 27.32, 22.34, 22.32.

ν_{max} (film/cm⁻¹): 2926 w, 2668 s, 1647 s, 1568 m, 1467 m, 1414 s, 1390 s.

2.116: Methyl 1-acetyl-1,2,2a,3,4,5-hexahydrobenzo[*cd*]indole-4-carboxylate



A glass syringe filled with a solution of AIBN (0.022g) and Bu_3SnH (0.566g, 1.95mmol) in toluene (50ml) connected to syringe pump equipped with a long needle was cautiously inserted through a suba-seal placed in the top of the reflux condenser connected to a flask containing a stirring solution of methyl (2*E*)-3-{3-[acetyl(allyl)amino]-2-bromophenyl}-2-propenoate (0.470g, 1.39mmol) and AIBN (0.011g) in toluene (20ml) at reflux. Once the entire solution had been added the reaction the syringe was removed and the solution was refluxed for 18hrs. The solution was concentrated under reduced pressure and the white residue was purified by column chromatography ($\text{MeOH}:\text{CH}_2\text{Cl}_2$, 1:99) to give a white solid which was triturated with diethyl ether producing **2.116** methyl 1-acetyl-1,2,2a,3,4,5-hexahydrobenzo[*cd*]indole-4-carboxylate (0.256g, 71%). $R_f = 0.22$ ($\text{MeOH}:\text{CH}_2\text{Cl}_2$, 1:99)

m/z (ESI): 282, 257, 140.

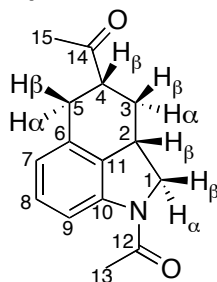
HRMS (ESI): Calcd. for $\text{C}_{15}\text{H}_{17}\text{N}_1\text{O}_3[\text{M}+\text{Na}^+]$: 282.1101; found: 282.1106.

^1H NMR (500 MHz, CDCl_3) δ : 7.84 (d, $J = 7.8$, 1H, H-9) 7.15 (t, $J = 7.8$, 1H, H-8), 6.84 (d, $J = 7.7$, 1H, H-7), 4.24 (t, $J = 9.2$, 1H, H-1 α), 3.76 (s, 3H, H-15), 3.61 (t, $J = 10.5$, 1H, H-1 β), 3.45 – 3.33 (m, 1H, H-2 β), 3.15 (dd, $J = 16.6$, 6.2, 1H, H-5 β), 2.91 (dd, $J = 16.7$, 11.6, 1H, H-5 α), 2.47 (d, $J = 11.3$, 1H, H-4 β), 2.47 (d, $J = 11.9$ Hz, H-3 β), 2.23 (s, 3H, H-13), 1.49 (dd, $J = 15.7$, 8.0 Hz, H-3 α).

^{13}C NMR (126 MHz, CDCl_3) δ : 175.36, 168.42, 141.65, 130.76, 129.05, 128.46, 122.75, 114.25, 77.26, 77.01, 76.75, 68.49, 56.65, 51.96, 40.53, 38.73, 37.35, 31.90, 30.31, 29.67, 29.36, 28.65, 23.88, 23.16, 22.66, 14.07, 10.98.

ν_{max} (film/ cm^{-1}): 2953 w, 1740 s, 1714 m, 1651 s, 1461 s, 1403 s.

2.117: Methyl (2*R*,3*E*)-5-{acetyl-2-bromo-3-[(1*E*)-3-oxo-1-butenyl]anilino}-2-[[[(benzyloxy)carbonyl]amino]-3-pentenoate.



A glass syringe filled with a solution of AIBN (0.031g) and Bu_3SnH (0.771g, 2.65mmol) in toluene (60ml) connected to syringe pump equipped with a long needle was *cautiously* inserted through a suba-seal placed in the top of the reflux condenser connected to a flask containing a stirring solution of *N*-allyl-*N*-{2-bromo-3-[(1*E*)-3-oxo-1-butenyl]phenyl}acetamide (0.610g, 1.89mmol) and AIBN (0.016g) in toluene (35ml) at reflux. Once the entire solution had been added the reaction the syringe was removed and the solution was refluxed for 18hrs. The solution was concentrated under reduced pressure and the white residue was purified by column chromatography ($\text{MeOH}:\text{CH}_2\text{Cl}_2$, 1:150) to a give a white solid which was triturated with diethyl ether producing **2.117** methyl (2*R*,3*E*)-5-{acetyl-2-bromo-3-[(1*E*)-3-oxo-1-butenyl]anilino}-2-[[[(benzyloxy)carbonyl]amino]-3-pentenoate (0.336g, 73%). R_f = 0.25 ($\text{MeOH}:\text{CH}_2\text{Cl}_2$, 1:150).

HRMS (ESI): Calcd. for $\text{C}_{15}\text{H}_{17}\text{NO}_2[\text{M}+\text{Na}^+]$: 266.1157; found: 266.1151

^1H NMR (500 MHz, CDCl_3) δ : 7.84 (d, J = 7.8, 1H, H-9), 7.15 (t, J = 7.8, 1H, H-8), 6.85 (d, J = 7.7, 1H, H-7), 4.25 (t, J = 9.2, 1H, H-1 α), 3.61 (t, J = 10.5, 1H, H-1 β), 3.41 (dd, J = 11.7, 11.4 Hz, 1H, H-4 β), 3.25 (m, 1H, H-2 β), 3.09 (dd, J = 6.1, 16.7, 1H, H-5 β), 2.83 (dd, J = 16.7, 11.4 Hz, 1H, H-4 β), 2.40 (dd, J = 12.2, 9.2 Hz, 1H, H-3 β), 2.28 (s, 3H, H-15), 2.23 (s, 3H, H-13), 1.49 (q, J = 11.7 Hz, 1H, H-3 α).

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Appendix A

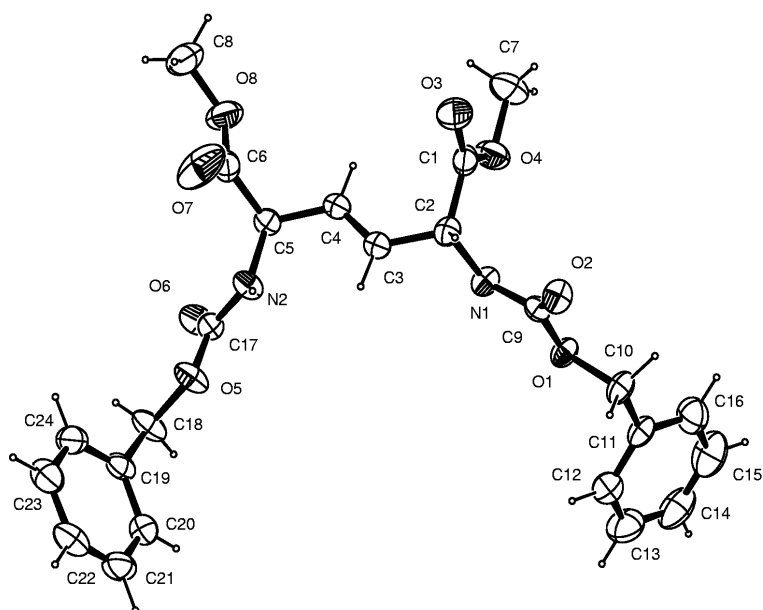


Table 1. Crystal data and structure refinement .

Identification code	mar1108	
Empirical formula	C ₂₄ H ₂₆ N ₂ O ₈	
Formula weight	470.47	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2 (No.5)	
Unit cell dimensions	a = 28.9290(17) Å	α = 90°.
	b = 4.7732(2) Å	β = 106.735(2)°.
	c = 17.8927(10) Å	γ = 90°.
Volume	2366.1(2) Å ³	
Z	4	
Density (calculated)	1.32 Mg/m ³	
Absorption coefficient	0.10 mm ⁻¹	
F(000)	992	
Crystal size	0.40 x 0.05 x 0.02 mm ³	
Theta range for data collection	3.44 to 25.95°.	
Index ranges	-35 ≤ h ≤ 28, -5 ≤ k ≤ 5, -18 ≤ l ≤ 22	
Reflections collected	8452	

Independent reflections	2545 [R(int) = 0.047]
Reflections with $I > 2\sigma(I)$	2148
Completeness to $\theta = 25.95^\circ$	98.1 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2545 / 1 / 317
Goodness-of-fit on F^2	1.049
Final R indices [$I > 2\sigma(I)$]	R1 = 0.039, wR2 = 0.081
R indices (all data)	R1 = 0.053, wR2 = 0.087
Largest diff. peak and hole	0.15 and -0.19 e. \AA^{-3}
The H atoms on N were refined.	

Data collection KappaCCD , Program package WinGX , Abs correction not applied,
Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for mar1108. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
O(1)	4839(1)	258(4)	2716(1)	32(1)
O(2)	4544(1)	-3484(4)	3202(1)	37(1)
O(3)	3832(1)	-835(6)	4864(1)	58(1)
O(4)	4334(1)	2473(5)	4674(1)	51(1)
O(5)	2116(1)	4424(4)	1002(1)	40(1)
O(6)	2339(1)	8244(4)	1752(1)	40(1)
O(7)	2024(1)	2336(7)	3319(2)	84(1)
O(8)	2374(1)	5817(6)	4085(1)	57(1)
N(1)	4223(1)	869(5)	3193(1)	30(1)
N(2)	2508(1)	3875(5)	2245(1)	32(1)
C(1)	4006(1)	476(7)	4439(2)	37(1)
C(2)	3859(1)	39(6)	3563(1)	31(1)
C(3)	3390(1)	1510(6)	3160(1)	28(1)
C(4)	3160(1)	3328(5)	3475(1)	28(1)
C(5)	2687(1)	4728(6)	3051(1)	29(1)
C(6)	2319(1)	4139(7)	3482(2)	37(1)
C(7)	4486(1)	3080(12)	5506(2)	74(1)
C(8)	2028(1)	5516(11)	4537(2)	71(1)
C(9)	4535(1)	-1014(6)	3053(1)	27(1)
C(10)	5188(1)	-1561(6)	2510(2)	37(1)
C(11)	5483(1)	312(6)	2159(2)	35(1)
C(12)	5297(1)	1395(8)	1415(2)	48(1)
C(13)	5562(1)	3220(9)	1106(2)	63(1)
C(14)	6022(1)	3979(8)	1533(2)	62(1)
C(15)	6208(1)	2900(9)	2256(2)	67(1)
C(16)	5942(1)	1083(8)	2570(2)	53(1)
C(17)	2321(1)	5724(6)	1679(1)	28(1)
C(18)	1887(1)	6200(6)	335(1)	43(1)
C(19)	1578(1)	4272(6)	-268(1)	34(1)
C(20)	1730(1)	3351(7)	-891(2)	41(1)
C(21)	1455(1)	1435(7)	-1417(2)	49(1)
C(22)	1028(1)	435(7)	-1325(2)	49(1)
C(23)	869(1)	1398(8)	-715(2)	49(1)

C(24)	1144(1)	3301(7)	-189(2)	41(1)
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Table 3. Bond lengths [\AA] and angles [$^\circ$] for mar1108.

O(1)-C(9)	1.346(3)
O(1)-C(10)	1.457(3)
O(2)-C(9)	1.207(3)
O(3)-C(1)	1.202(3)
O(4)-C(1)	1.325(4)
O(4)-C(7)	1.455(3)
O(5)-C(17)	1.338(3)
O(5)-C(18)	1.457(3)
O(6)-C(17)	1.210(3)
O(7)-C(6)	1.187(4)
O(8)-C(6)	1.316(3)
O(8)-C(8)	1.463(4)
N(1)-C(9)	1.346(3)
N(1)-C(2)	1.453(3)
N(2)-C(17)	1.335(3)
N(2)-C(5)	1.443(3)
C(1)-C(2)	1.515(4)
C(2)-C(3)	1.514(4)
C(3)-C(4)	1.314(4)
C(4)-C(5)	1.515(3)
C(5)-C(6)	1.511(4)
C(10)-C(11)	1.493(4)
C(11)-C(16)	1.371(4)
C(11)-C(12)	1.384(4)
C(12)-C(13)	1.378(5)
C(13)-C(14)	1.379(5)
C(14)-C(15)	1.352(5)
C(15)-C(16)	1.382(5)
C(18)-C(19)	1.502(4)
C(19)-C(20)	1.381(4)
C(19)-C(24)	1.385(4)
C(20)-C(21)	1.387(4)
C(21)-C(22)	1.377(5)
C(22)-C(23)	1.380(4)
C(23)-C(24)	1.382(4)

C(9)-O(1)-C(10)	115.8(2)
C(1)-O(4)-C(7)	116.4(3)
C(17)-O(5)-C(18)	116.7(2)
C(6)-O(8)-C(8)	116.9(3)
C(9)-N(1)-C(2)	121.0(2)
C(17)-N(2)-C(5)	121.5(2)
O(3)-C(1)-O(4)	124.6(3)
O(3)-C(1)-C(2)	122.5(3)
O(4)-C(1)-C(2)	112.9(2)
N(1)-C(2)-C(3)	108.9(2)
N(1)-C(2)-C(1)	114.1(2)
C(3)-C(2)-C(1)	112.1(2)
C(4)-C(3)-C(2)	126.6(2)
C(3)-C(4)-C(5)	124.8(2)
N(2)-C(5)-C(6)	110.7(2)
N(2)-C(5)-C(4)	112.9(2)
C(6)-C(5)-C(4)	109.3(2)
O(7)-C(6)-O(8)	123.5(3)
O(7)-C(6)-C(5)	124.8(3)
O(8)-C(6)-C(5)	111.6(2)
O(2)-C(9)-N(1)	125.7(2)
O(2)-C(9)-O(1)	124.3(2)
N(1)-C(9)-O(1)	110.0(2)
O(1)-C(10)-C(11)	105.7(2)
C(16)-C(11)-C(12)	117.6(3)
C(16)-C(11)-C(10)	121.2(3)
C(12)-C(11)-C(10)	121.2(3)
C(13)-C(12)-C(11)	121.0(3)
C(12)-C(13)-C(14)	120.3(3)
C(15)-C(14)-C(13)	119.0(3)
C(14)-C(15)-C(16)	120.9(3)
C(11)-C(16)-C(15)	121.2(3)
O(6)-C(17)-N(2)	125.5(2)
O(6)-C(17)-O(5)	123.5(2)
N(2)-C(17)-O(5)	111.0(2)
O(5)-C(18)-C(19)	105.5(2)
C(20)-C(19)-C(24)	118.9(3)
C(20)-C(19)-C(18)	120.9(3)

C(24)-C(19)-C(18)	120.1(2)
C(19)-C(20)-C(21)	120.3(3)
C(22)-C(21)-C(20)	120.4(3)
C(21)-C(22)-C(23)	119.5(3)
C(22)-C(23)-C(24)	120.1(3)
C(23)-C(24)-C(19)	120.7(3)

Hydrogen bonds with $H \cdots A < r(A) + 2.000$ Angstroms and $\angle DHA > 110$ deg.

D-H	d(D-H)	d(H...A)	$\angle DHA$	d(D...A)	A
N1-H1X	0.87	1.99	169	2.849	O2 [x, y+1, z]
N2-H2X	0.89	1.95	168	2.828	O6 [x, y-1, z]

Appendix B

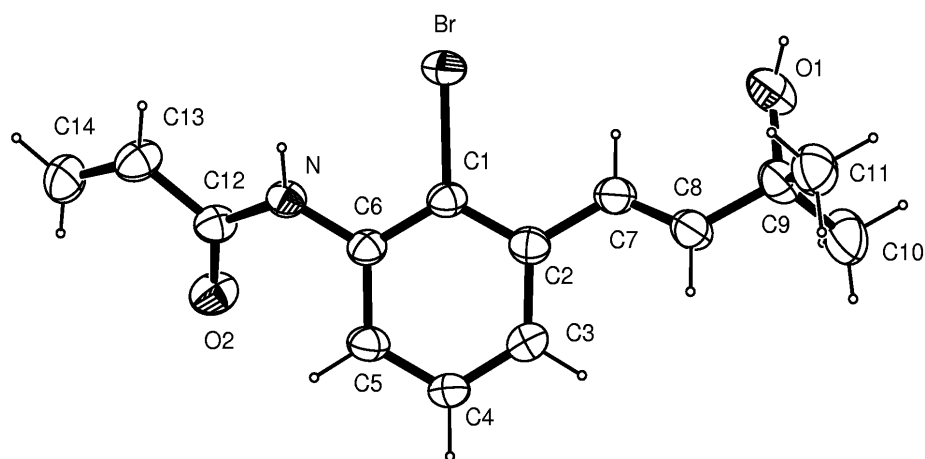


Table 1. Crystal data and structure refinement .

Identification code	feb1908	
Empirical formula	C ₁₄ H ₁₆ Br N O ₂	
Formula weight	310.19	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P $\bar{1}$ (No.2)	
Unit cell dimensions	a = 9.3923(4) Å	α = 100.511(2)°.
	b = 9.9224(4) Å	β = 102.992(2)°.
	c = 16.4652(5) Å	γ = 92.468(2)°.
Volume	1464.42(10) Å ³	
Z	4	
Density (calculated)	1.41 Mg/m ³	
Absorption coefficient	2.80 mm ⁻¹	
F(000)	632	
Crystal size	0.30 x 0.30 x 0.25 mm ³	
Theta range for data collection	3.47 to 25.89°.	
Index ranges	-11 ≤ h ≤ 11, -12 ≤ k ≤ 12, -20 ≤ l ≤ 20	
Reflections collected	23899	

Independent reflections	5656 [R(int) = 0.072]
Reflections with I>2sigma(I)	4054
Completeness to theta = 25.89°	99.3 %
Tmax. and Tmin.	0.476 and 0.401
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	5656 / 0 / 325
Goodness-of-fit on F ²	1.120
Final R indices [I>2sigma(I)]	R1 = 0.074, wR2 = 0.242
R indices (all data)	R1 = 0.106, wR2 = 0.258
Largest diff. peak and hole	1.49 and -0.72 e.Å ⁻³ (near Br)

There are two independent molecules with essentially the same geometry.

The hydroxyl H atoms are disordered over two sites.

Data collection KappaCCD , Program package WinGX , Abs correction MULTISCAN

Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for feb1908. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
Br	5181(1)	1170(1)	2963(1)	47(1)
O(1)	5960(8)	5878(7)	4695(4)	55(2)
O(2)	723(6)	-1406(6)	919(4)	45(2)
N	3056(7)	-411(7)	1366(4)	33(2)
C(1)	3606(8)	1865(8)	2258(5)	32(2)
C(2)	3345(9)	3259(9)	2463(5)	33(2)
C(3)	2125(10)	3684(9)	1950(6)	42(2)
C(4)	1274(10)	2818(9)	1246(6)	41(2)
C(5)	1586(9)	1458(9)	1039(5)	36(2)
C(6)	2751(8)	967(8)	1552(5)	31(2)
C(7)	4252(9)	4224(9)	3206(5)	38(2)
C(8)	4375(10)	5580(10)	3297(5)	42(2)
C(9)	5262(11)	6582(10)	4047(6)	46(2)
C(10)	4265(12)	7559(12)	4420(8)	67(3)
C(11)	6448(12)	7385(11)	3779(7)	53(2)
C(12)	2051(8)	-1506(9)	1067(5)	34(2)
C(13)	2666(10)	-2862(9)	924(6)	43(2)
C(14)	1806(12)	-4004(10)	606(6)	50(2)
Br(1B)	10353(1)	7324(1)	2805(1)	47(1)
O(1B)	10959(8)	3963(8)	4693(4)	61(2)
O(2B)	5804(7)	8661(7)	1212(6)	65(2)
N(1B)	8042(7)	7876(7)	1312(5)	37(2)
C(1B)	8627(9)	6163(8)	2199(5)	33(2)
C(2B)	8322(9)	4938(9)	2448(5)	36(2)
C(3B)	6997(10)	4168(9)	2004(5)	39(2)
C(4B)	6076(10)	4579(9)	1333(6)	40(2)
C(5B)	6420(9)	5790(9)	1093(5)	37(2)
C(6B)	7686(9)	6601(8)	1525(5)	33(2)
C(7B)	9248(9)	4495(9)	3184(6)	40(2)
C(8B)	9233(10)	3237(10)	3328(6)	44(2)
C(9B)	10155(10)	2773(10)	4094(6)	43(2)
C(10B)	11225(13)	1821(12)	3817(7)	60(3)
C(11B)	9160(14)	2068(15)	4522(8)	77(4)

C(12B)	7098(9)	8842(9)	1187(6)	37(2)
C(13B)	7721(10)	10119(9)	1010(6)	41(2)
C(14B)	6872(12)	11070(10)	775(6)	50(2)

Table 3. Bond lengths [\AA] and angles [$^\circ$] for feb1908.

Br-C(1)	1.903(8)
O(1)-C(9)	1.432(11)
O(2)-C(12)	1.228(10)
N-C(12)	1.350(10)
N-C(6)	1.402(10)
C(1)-C(6)	1.390(11)
C(1)-C(2)	1.408(11)
C(2)-C(3)	1.393(12)
C(2)-C(7)	1.475(12)
C(3)-C(4)	1.370(12)
C(4)-C(5)	1.391(12)
C(5)-C(6)	1.389(11)
C(7)-C(8)	1.324(13)
C(8)-C(9)	1.492(12)
C(9)-C(10)	1.521(14)
C(9)-C(11)	1.532(14)
C(12)-C(13)	1.488(12)
C(13)-C(14)	1.314(13)
Br(1B)-C(1B)	1.909(8)
O(1B)-C(9B)	1.449(12)
O(2B)-C(12B)	1.231(10)
N(1B)-C(12B)	1.346(11)
N(1B)-C(6B)	1.418(11)
C(1B)-C(2B)	1.390(12)
C(1B)-C(6B)	1.404(11)
C(2B)-C(3B)	1.404(12)
C(2B)-C(7B)	1.473(12)
C(3B)-C(4B)	1.379(12)
C(4B)-C(5B)	1.380(12)
C(5B)-C(6B)	1.377(12)
C(7B)-C(8B)	1.313(13)
C(8B)-C(9B)	1.520(12)
C(9B)-C(10B)	1.497(14)
C(9B)-C(11B)	1.510(14)
C(12B)-C(13B)	1.477(12)
C(13B)-C(14B)	1.317(13)

C(12)-N-C(6)	125.8(7)
C(6)-C(1)-C(2)	122.2(7)
C(6)-C(1)-Br	118.3(6)
C(2)-C(1)-Br	119.5(6)
C(3)-C(2)-C(1)	116.6(8)
C(3)-C(2)-C(7)	120.6(8)
C(1)-C(2)-C(7)	122.7(7)
C(4)-C(3)-C(2)	121.9(8)
C(3)-C(4)-C(5)	120.3(8)
C(6)-C(5)-C(4)	120.0(8)
C(5)-C(6)-C(1)	118.8(7)
C(5)-C(6)-N	120.8(7)
C(1)-C(6)-N	120.4(7)
C(8)-C(7)-C(2)	125.3(8)
C(7)-C(8)-C(9)	126.5(9)
O(1)-C(9)-C(8)	110.5(8)
O(1)-C(9)-C(10)	107.9(8)
C(8)-C(9)-C(10)	109.6(8)
O(1)-C(9)-C(11)	108.6(8)
C(8)-C(9)-C(11)	109.7(8)
C(10)-C(9)-C(11)	110.5(9)
O(2)-C(12)-N	123.2(8)
O(2)-C(12)-C(13)	121.7(8)
N-C(12)-C(13)	115.1(7)
C(14)-C(13)-C(12)	121.2(8)
C(12B)-N(1B)-C(6B)	124.4(7)
C(2B)-C(1B)-C(6B)	122.2(8)
C(2B)-C(1B)-Br(1B)	119.5(6)
C(6B)-C(1B)-Br(1B)	118.2(6)
C(1B)-C(2B)-C(3B)	116.5(8)
C(1B)-C(2B)-C(7B)	123.2(8)
C(3B)-C(2B)-C(7B)	120.1(8)
C(4B)-C(3B)-C(2B)	121.7(8)
C(3B)-C(4B)-C(5B)	120.3(8)
C(6B)-C(5B)-C(4B)	120.2(8)
C(5B)-C(6B)-C(1B)	119.0(8)
C(5B)-C(6B)-N(1B)	121.4(7)

C(1B)-C(6B)-N(1B)	119.6(7)
C(8B)-C(7B)-C(2B)	125.5(9)
C(7B)-C(8B)-C(9B)	126.0(9)
O(1B)-C(9B)-C(10B)	109.0(8)
O(1B)-C(9B)-C(11B)	108.8(9)
C(10B)-C(9B)-C(11B)	110.7(10)
O(1B)-C(9B)-C(8B)	109.3(8)
C(10B)-C(9B)-C(8B)	109.7(8)
C(11B)-C(9B)-C(8B)	109.3(8)
O(2B)-C(12B)-N(1B)	122.0(8)
O(2B)-C(12B)-C(13B)	122.8(8)
N(1B)-C(12B)-C(13B)	115.2(7)
C(14B)-C(13B)-C(12B)	120.9(9)

Hydrogen bonds with $H \cdots A < r(A) + 2.000$ Angstroms and $\angle DHA > 110$ deg.

D-H	d(D-H)	d(H...A)	$\angle DHA$	d(D...A)	A
O1-H1XA y+1, -z+1]	0.853	1.976	179.19	2.830	O1B_a [-x+2, -
O1-H1XB z+1]	0.849	2.064	179.54	2.912	O1 [-x+1, -y+1, -
N-H0]	0.880	1.988	158.79	2.826	O2B_a [x, y-1, z
O1B-H1BX_a z+1]	0.852	1.978	179.18	2.830	O1 [-x+2, -y+1, -
O1B-H1BY_a y+1, -z+1]	0.850	2.130	179.49	2.980	O1B_a [-x+2, -
N1B-H1B1_a	0.880	1.966	167.16	2.831	O2 [x+1, y+1, z]

